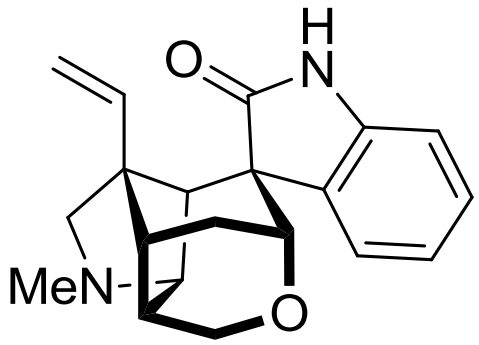
Total Synthesis of (+)-Gelsemine

Xuan

Dong group seminar

12/19/2012

Historical Background of Gelsemine

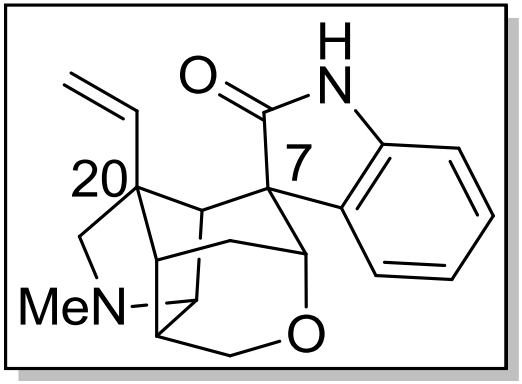


Gelsemine

- First detected the presence of alk aloids in extracts of *G. sempervir ens* in 1870 by Wormley.
- 1876, Sonnenschein isolated gels emine as the principal componen t of *G. sempervirens*
- The correct molecular formula o f gelsemine, $C_{20}H_{22}N_2O_2$, was est ablished in 1910 by moore.

Wormley, T. G. Am. *J. Pharm*. **1870**, *42*, 1-16; Sonnenschein, F. L. *Ber*. **1876**, *9*, 1182-1186; Moorc, C. W. *J. Chem. Soc*. **1910**, *97*, 2223-2233.

Gelsemine: A Synthetic Challenge



Structural Challenge:

- Seven contiguous stereocenters
- [3.2.1] bicyclic system
- Spirooxindole system
- very little functionality

Structure determinstion:

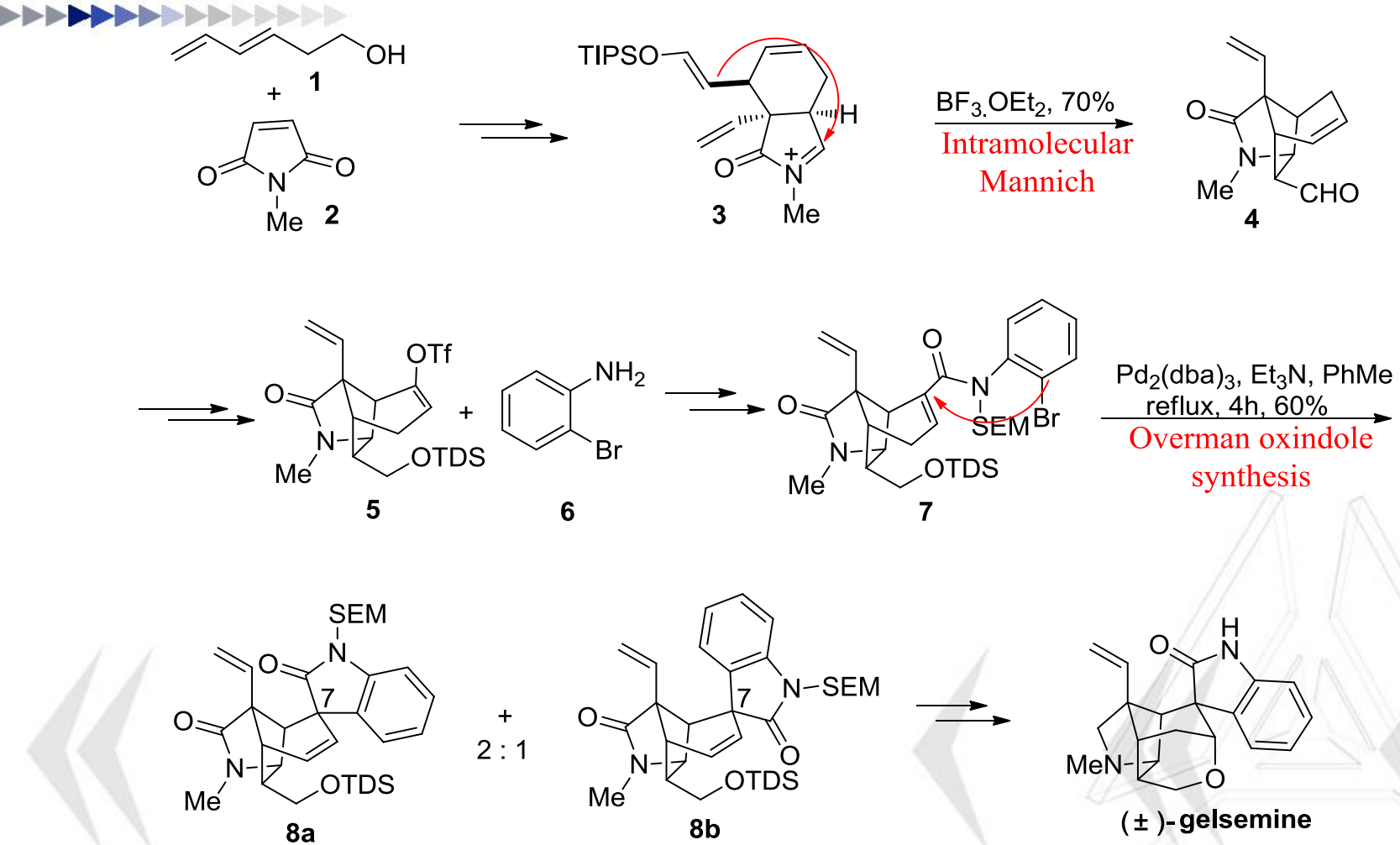
Structure determined independently by the groups of Conroy and Wilson in 1959 via NMR and X-ray crystallography.

Synthetic Interest:

- Racemic total syntheses:
  Speckamp, W. N. (1994)
  Johnson, A. P. (1994)
  Fukuyama, T. (1996)
  Hart, D. J. (1997)
  Overman (1999)
  Danishefsky (2002)
- Enantioselective total synthesis:
  Fukuyama (2000)

Chakrabarti, J. K. *Tetrahedron Lett*.**1959**, *1* (4), 6−13; Lovell, F. M.; Pepinsky, R.; Wilson, A. J. C. *Tetrahedron Lett*. **1959**, *1*, 1−5; Lin, H.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 36−51

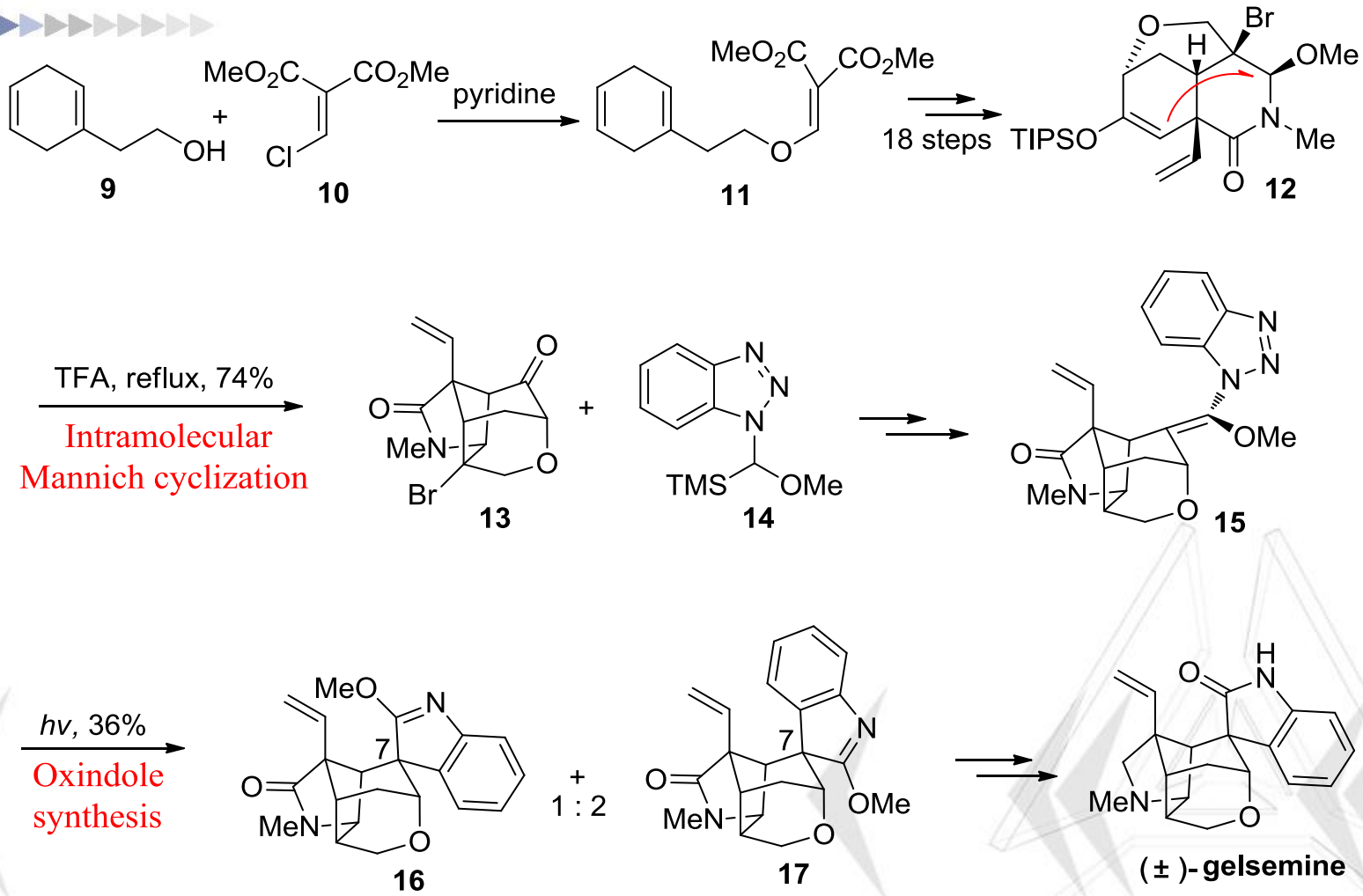
Speckamp and Hiemstra's Total Synthesis of (±)-Gelsemine



19 steps, 0.83% overall yield

Speckamp et al, *J. Chem. Soc., Chem. Commun.* **1994**, 767

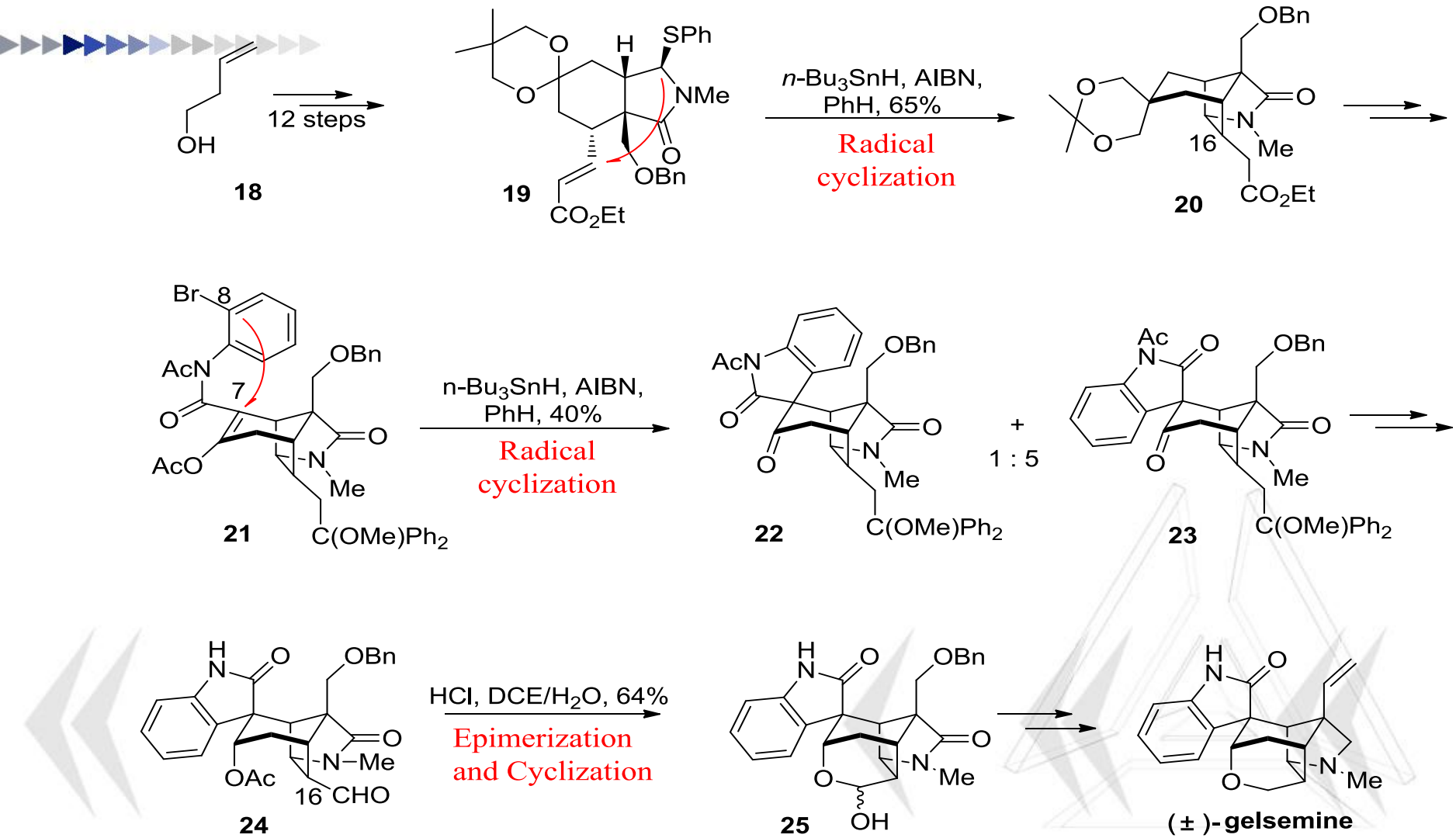
Johnson's Total Synthesis of (±)-Gelsemine



29 steps, 0.58% overall yield

Johnson, A. P. *J. Chem. Soc., Chem. Commun.* **1994**, 763

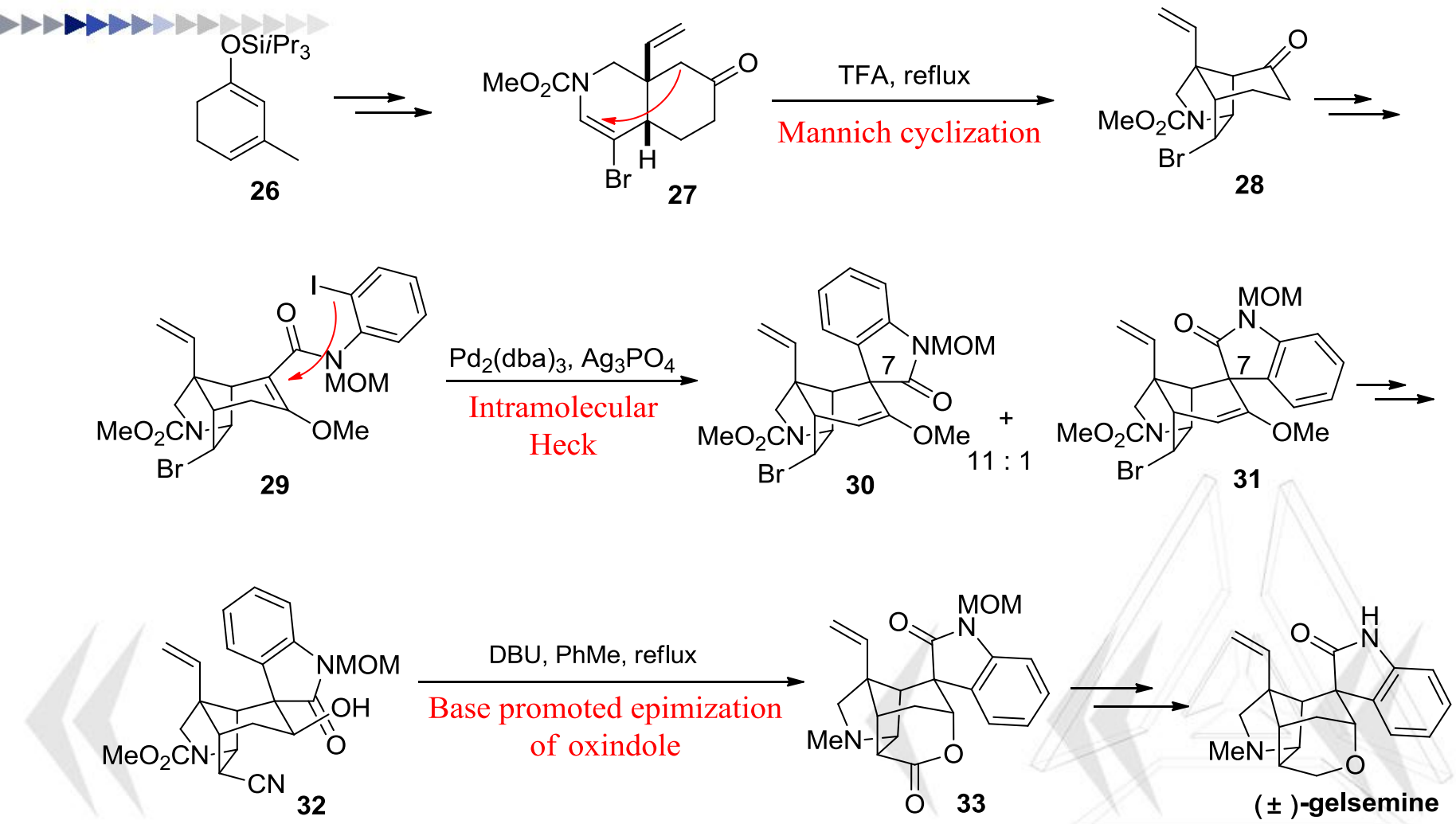
Hart's Total Synthesis of (±)-Gelsemine



23 steps, 0.25% overall yield

Hart, D. J et al. *J. Am. Chem. Soc.* **1997**, *119*, 6226

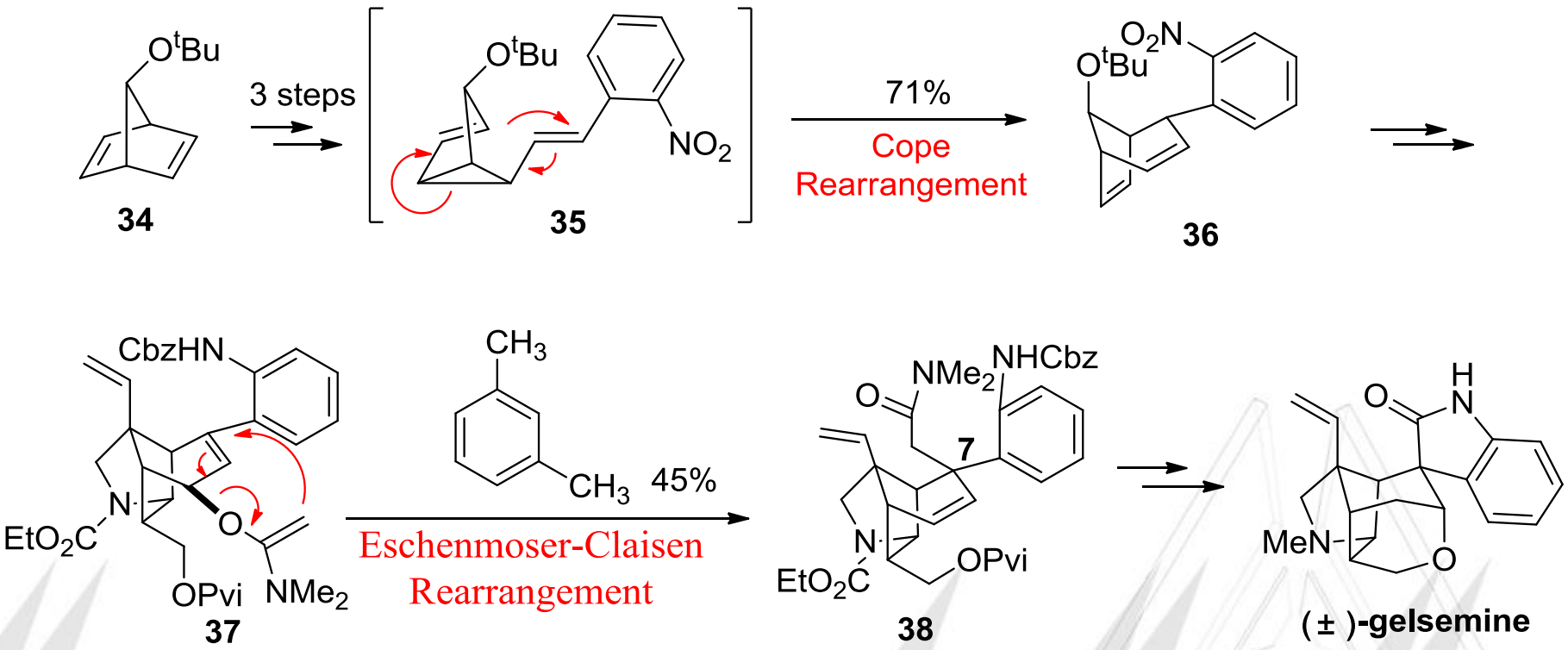
Overman's Total Synthesis of (±)-Gelsemine



26 steps, 1.2% overall yield

Overman, L. E et al. *Angew. Chem., Int. Ed.* **1999**, *38*, 2934

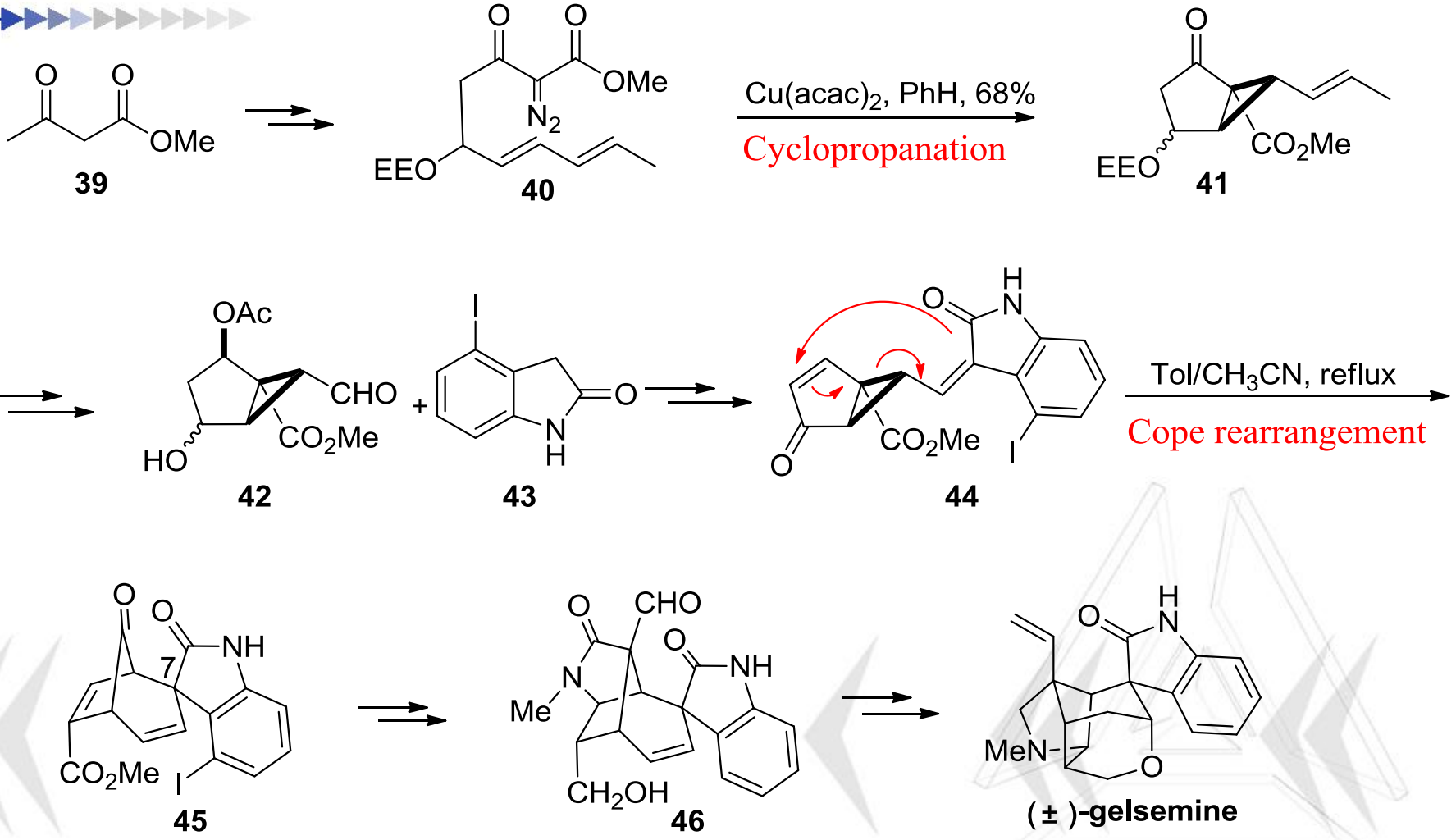
Danishefsky's Total Synthesis of (±)-Gelsemine



36 steps, 0.02% overall yield

Danishefsky, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 9812

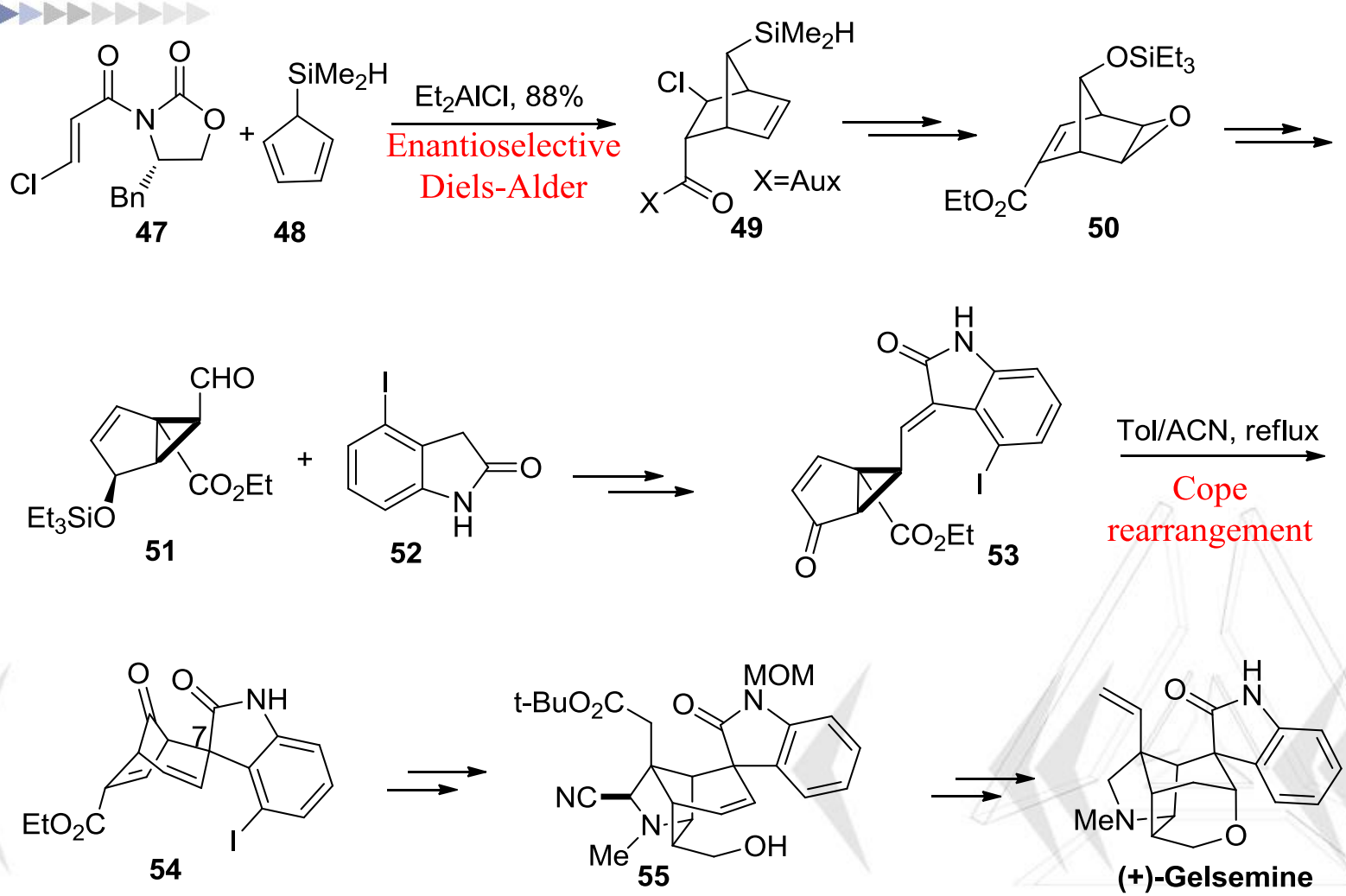
Fukuyama's Total Synthesis of (±)-Gelsemine



32 steps, 0.67% overall yield

T. Fukuyama, G. Liu, *J. Am. Chem. Soc.* **1996**, *118*, 7426−7427

Fukuyama's Enantioselective Total Synthesis of (+)-Gelsemine



31 steps, 0.86% overall yield

Fukuyama, T et al. *Angew. Chem., Int. Ed.* **2000**, *39*, 4073

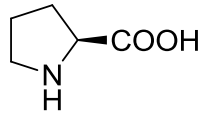
Why we synthesis Gelsemine?

	Bicyclo-[3.2.1] skeleton	Spirooxindole structure	Tetrahydropyran ring	Pyrrolidine ring	Yield
Speckamp 1994	Intramolecular Mannich	Intramolecular Heck	Intramolecular oxymercuration		19 steps 0.83%
Johnson 1994	Intramolecular Mannich	Radical cyclization		Intramolecular Mannich	29 steps 0.58%
Fukuyama 1996	Cope rearrangement	Cope rearrangement	Intramolecular oxymercuration		32 steps 0.67%
Hart 1997	Radical cyclization	Radical cyclization	Intramolecular Hemiacetal formation		23 steps 0.25%
Overman 1999	Intramolecular Mannich	Intramolecular Heck	Intramolecular lactone formation	Intramolecular Mannich	26 steps 1.2%
Danishefsky 2002	Cope rearrangement	[3,3]-Claisen rearrangement	Intramolecular oxymercuration	Oxetane ring opening	36 steps 0.019%
Fukuyama 2000	Cope rearrangement	Cope rearrangement	Intramolecular oxymercuration	Intramolecular Michael	31 steps 0.86%

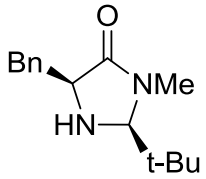
Key strategy in synthesis of Gelsemine

Organocatalysis: a new stream in organic synthesis

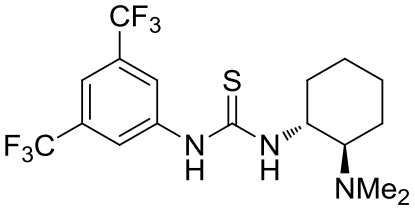
Org. cat:



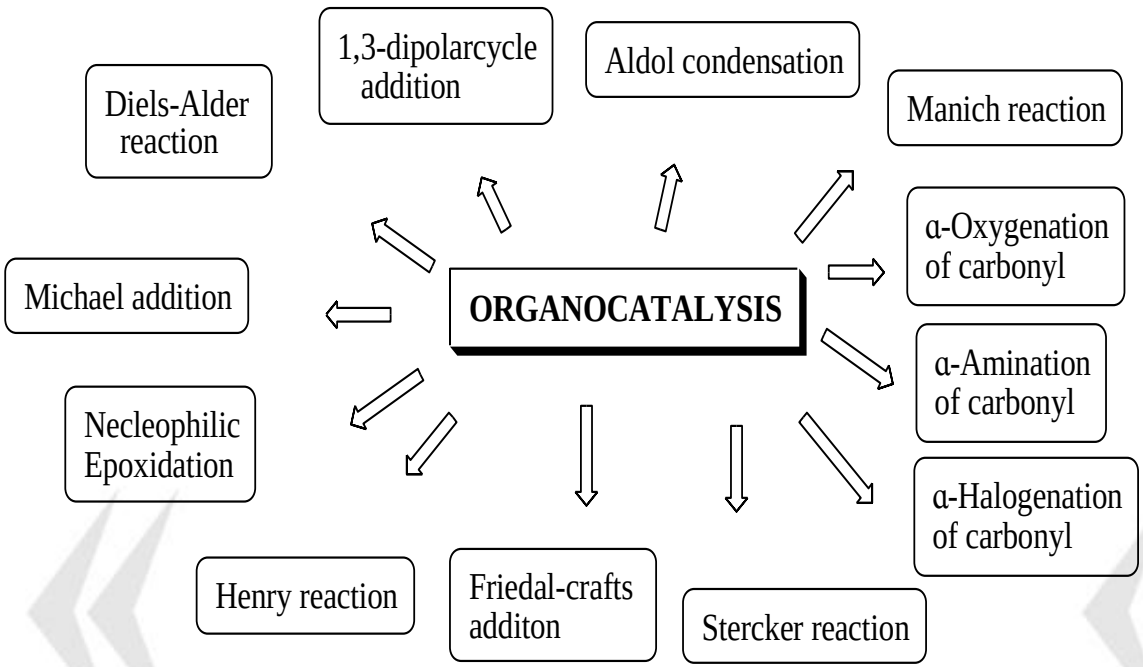
Proline



Imidazolidinone



Thiourea



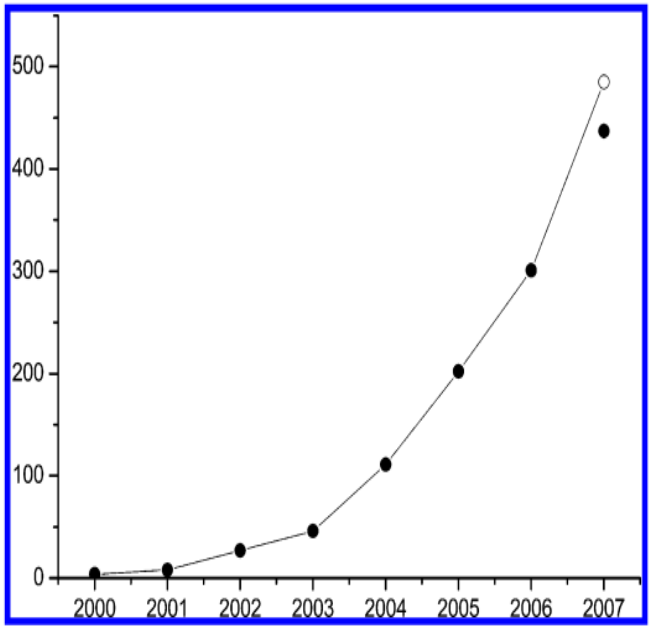
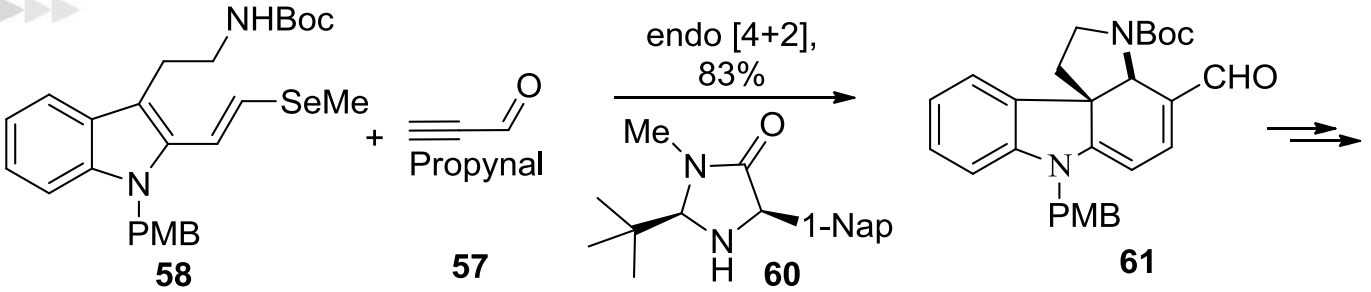


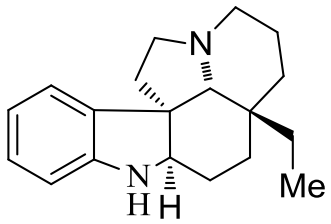
Figure 1. Number of publications using the term "organocatalysis" in the title or abstract since the year 2000: ●, from SciFinder as of November 21, 2007; ○, predicted.

Pihko, P. M et al. . *Chem. Rev*. **2007**, *107*, 5416- 5470

List, B et al.. *Chem. Rev*. **2007**, *107*, 5471- 5569

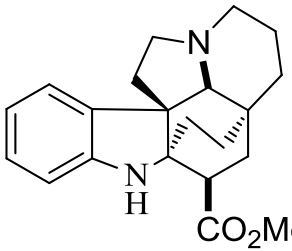
Synthesis of natural products by means of organo catalysis





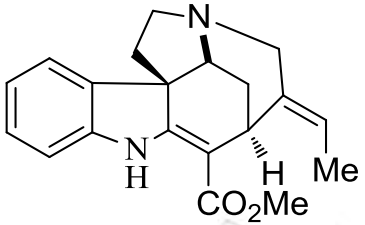
(+)-aspidospermidine

9 steps 24% overall yield



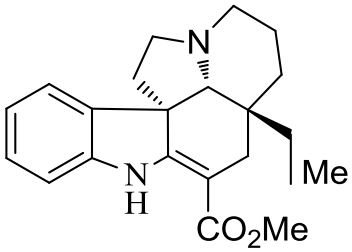
(-)-kopsinine

9 steps 14% overall yield



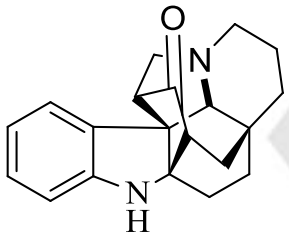
(-)-akuammicine

10 steps 10% overall yield



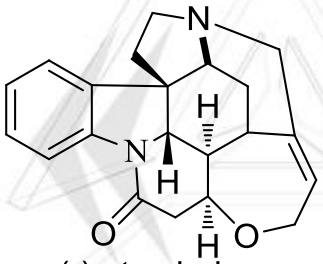
(+)-vincadifformine

11 steps 8.9% overall yield



(-)-kopsanone

11 steps 10% overall yield

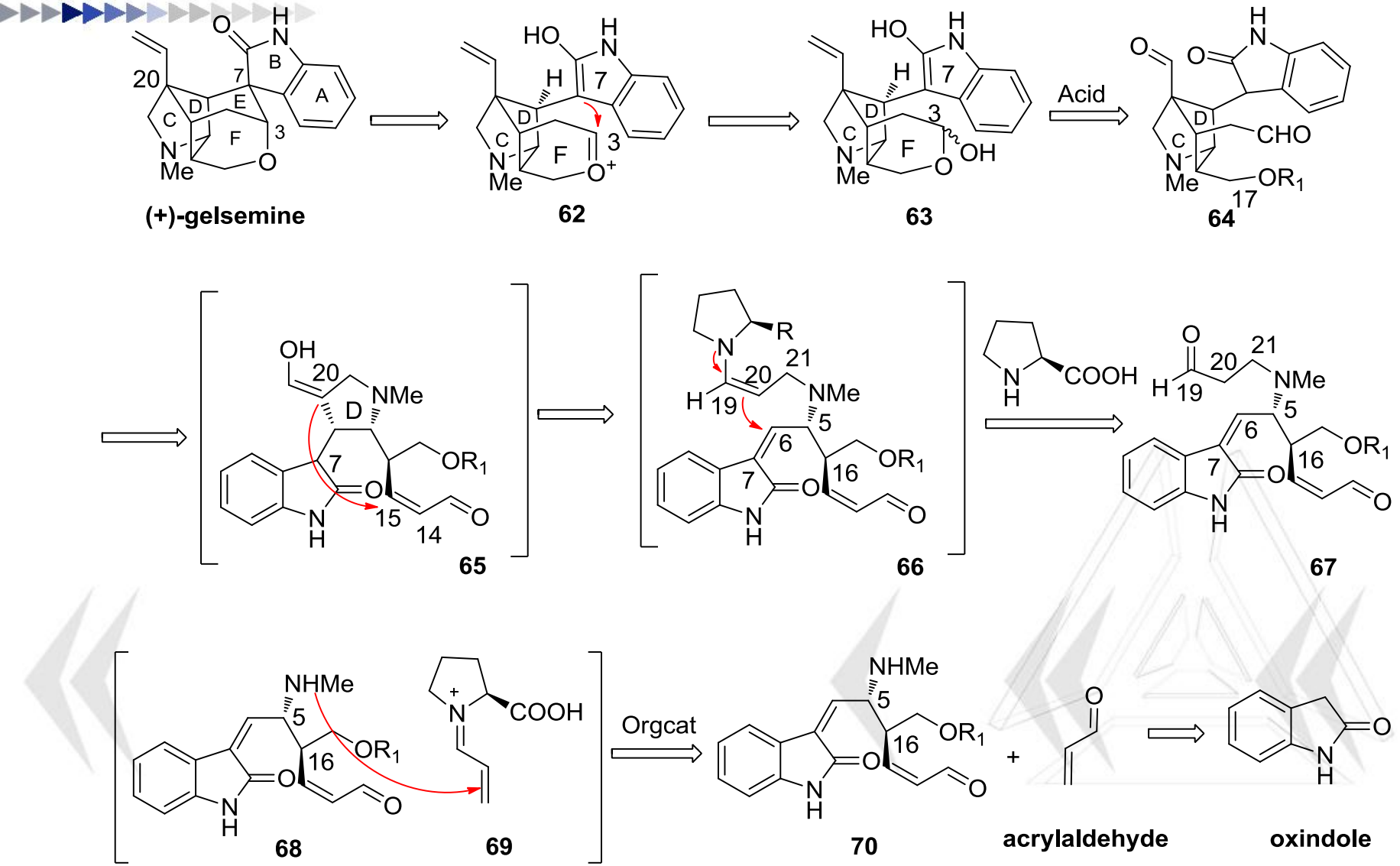


(-)-strychnine

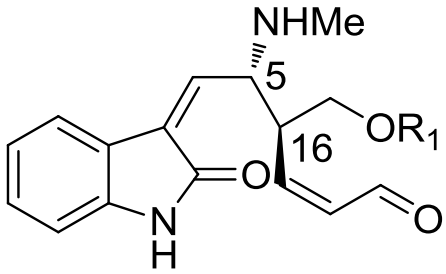
12 steps 6.4% overall yield

MacMillan.W. C et al. *Nature*, **2011**, *475*, 183-188

Retro-synthetic Analysis of (+)-Gelsemine



Synthesis the key structure of gelsemine by organocatalysis



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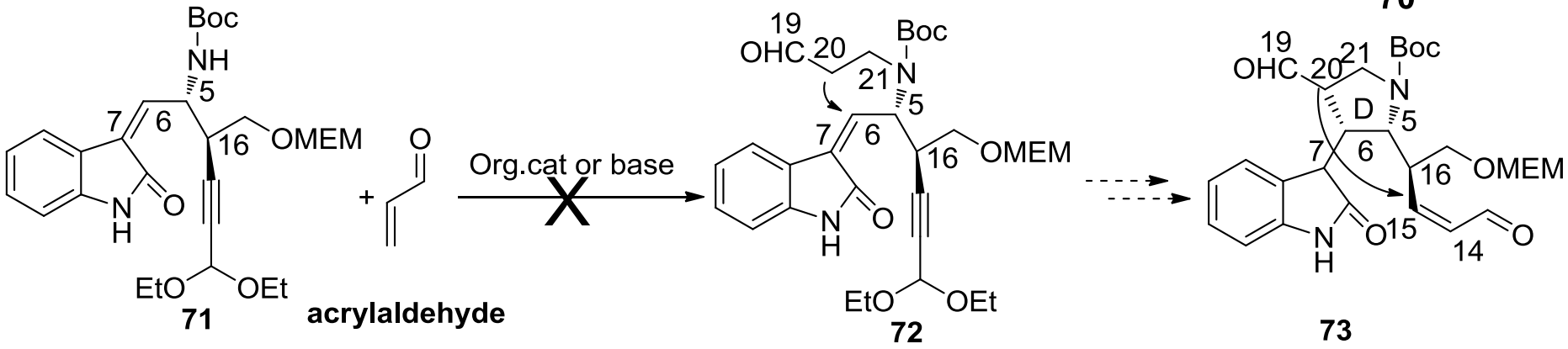
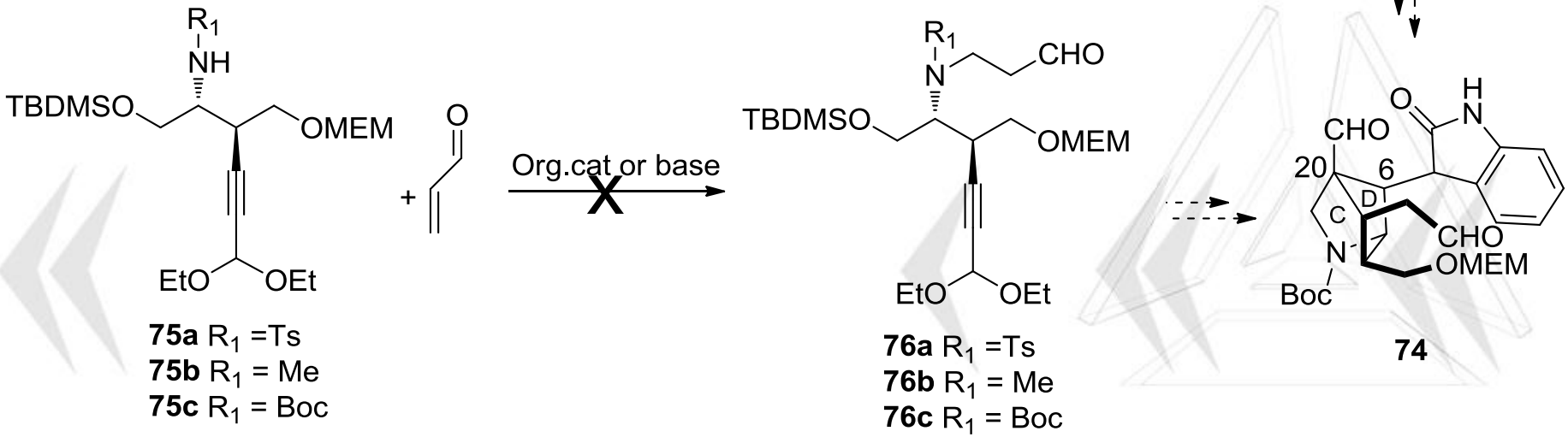
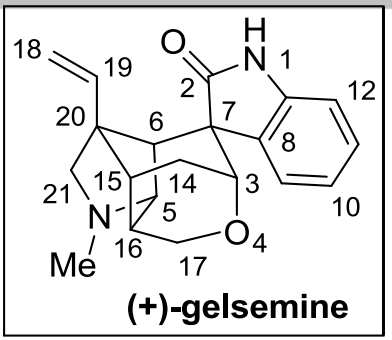


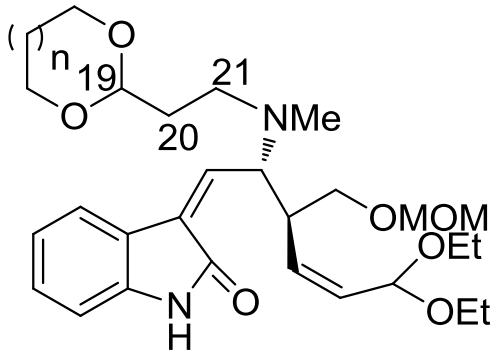


75a R_1 =Ts
75b R_1 = Me
75c R_1 = Boc

76a R_1 =Ts
76b R_1 = Me
76c R_1 = Boc

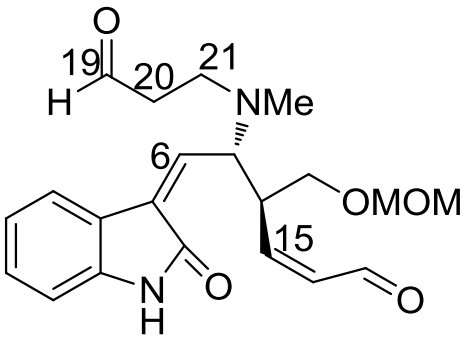
Synthesis the Key Structure of (+)-Gelsemine





78 n = 0
79 n = 1

acid



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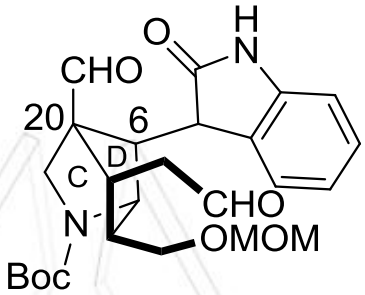
Orgcat



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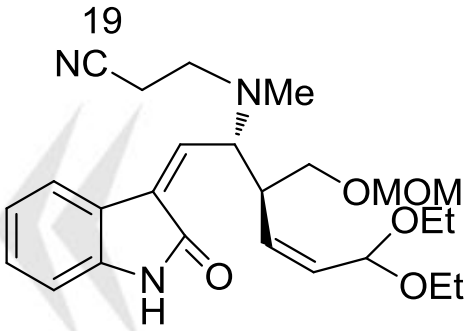
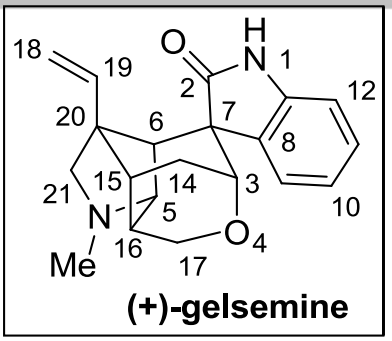
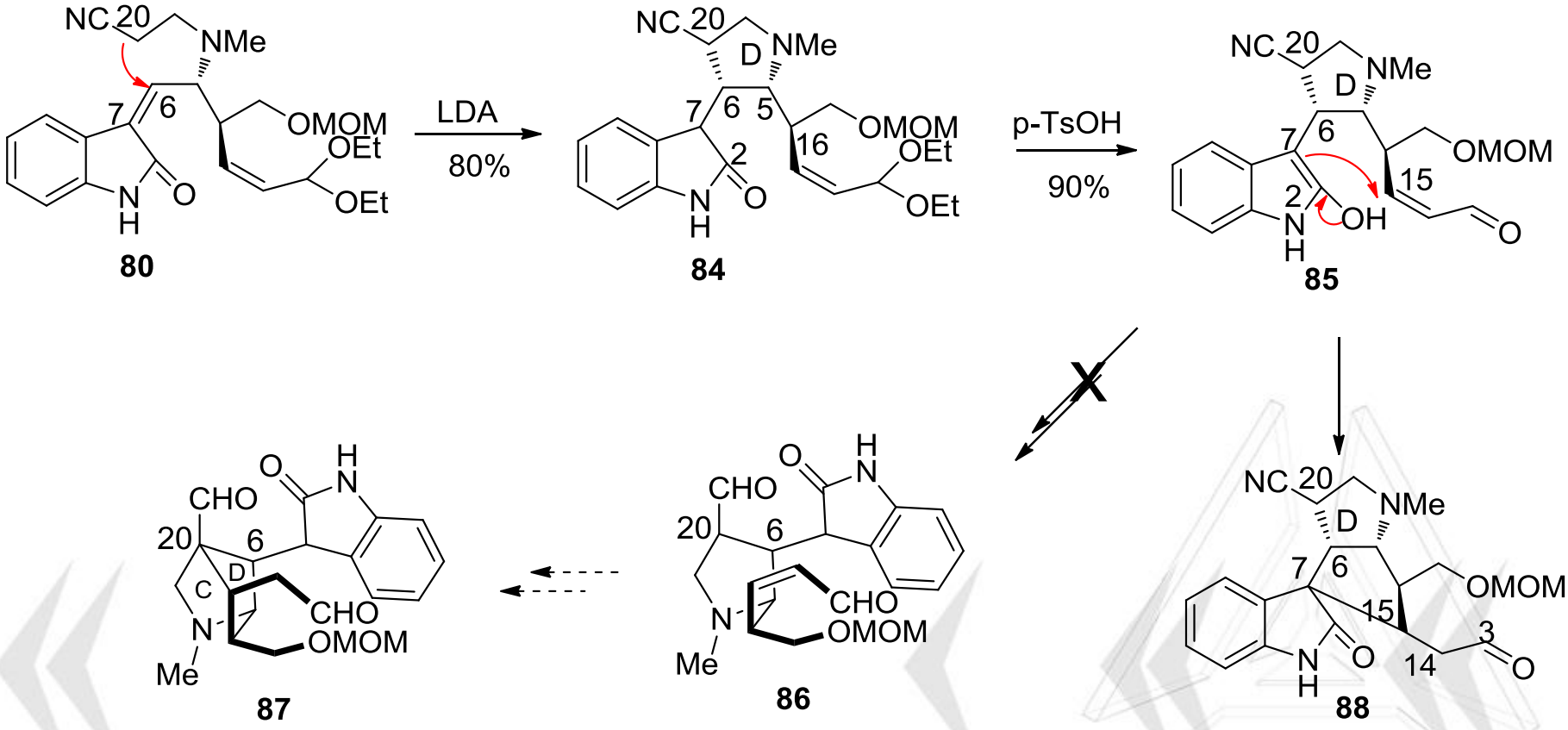


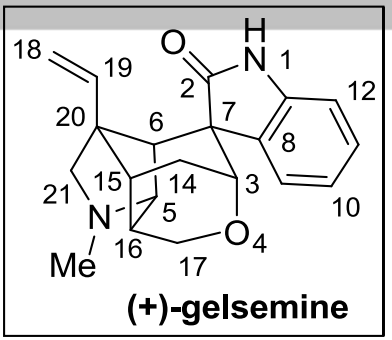
80

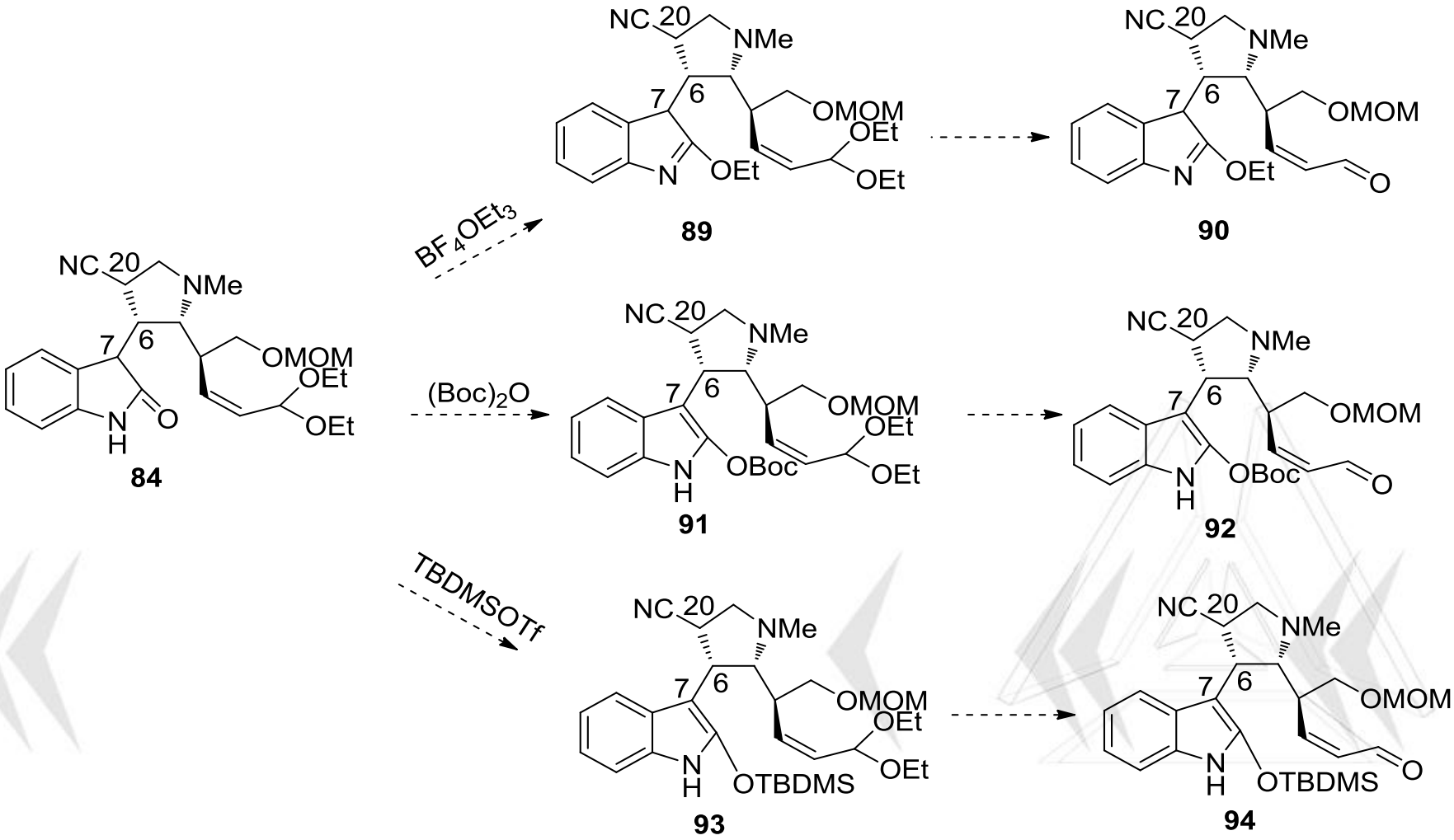
Synthesis D-ring and C-ring of (+)-gelsemine

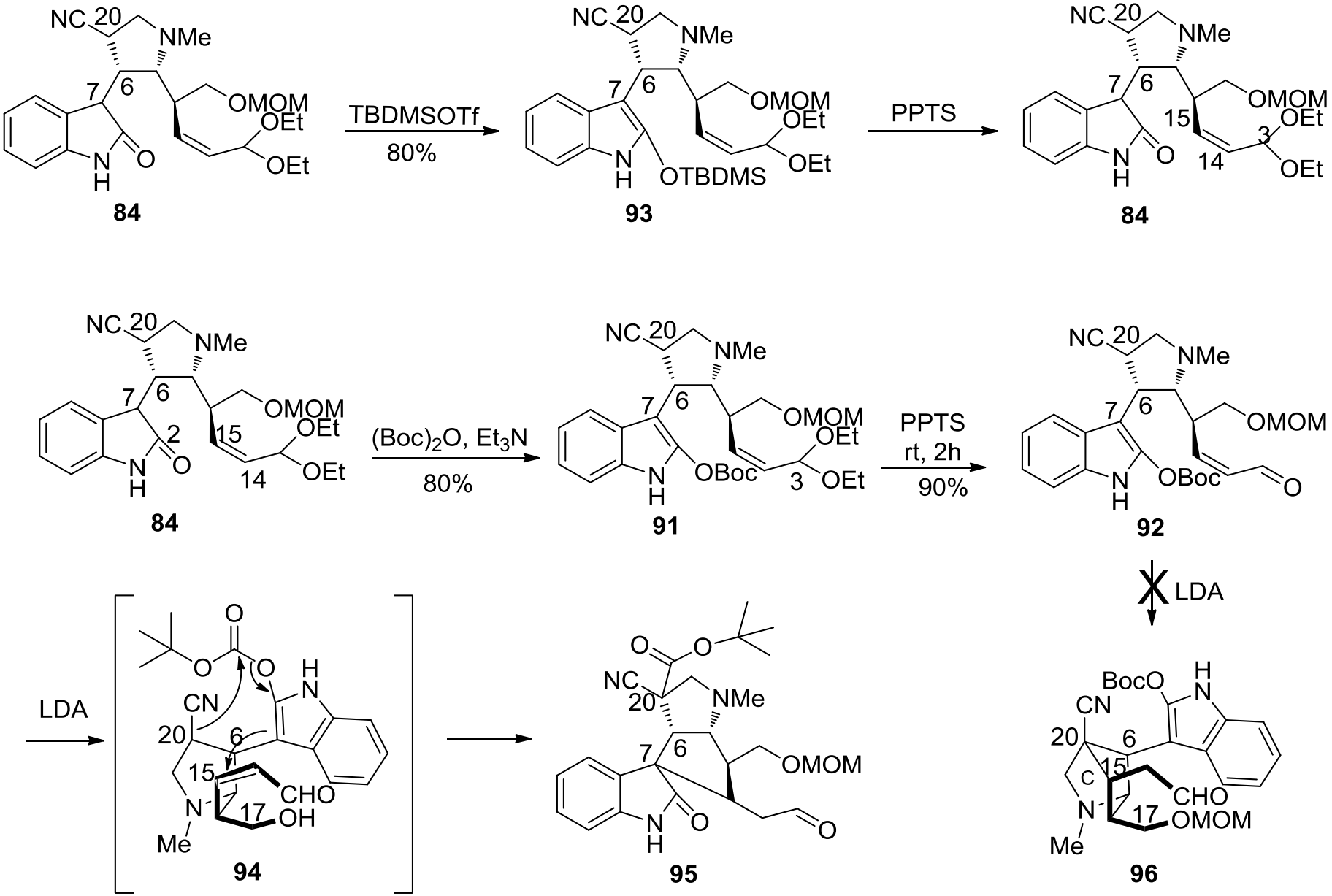




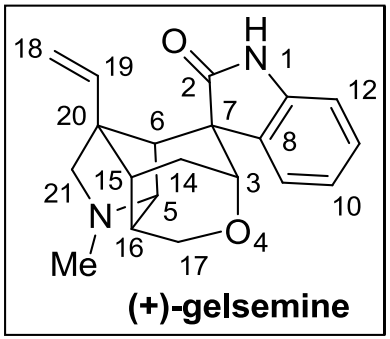
Total Synthesis of (+)-Gelsemine

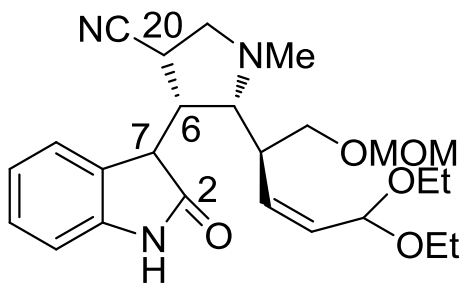





NC
20
NMe
7
6
OMOM
OEt
OEt
N
H
O
84
TBDMSOTf
80%
OTBDMS
93
PPTS
15
14
3
(Boc)2O, Et3N
OBoc
91
rt, 2h
90%
92
LDA
BocO
CN
CHO
OH
17
Me
94
95
96

Total Synthesis of (+)-Gelsemine

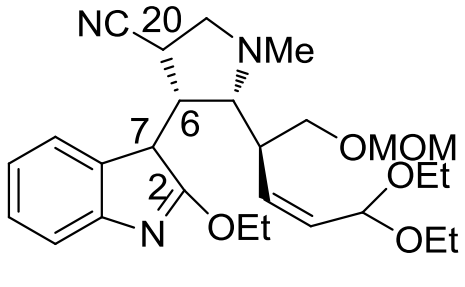




84

BF_4OEt_3, DIPEA

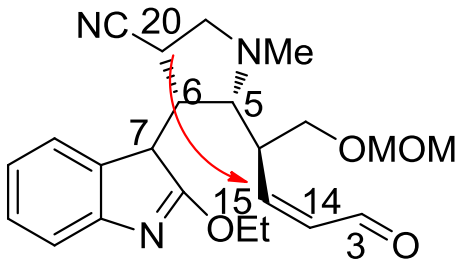
80%



89

PPTS
rt, 2h

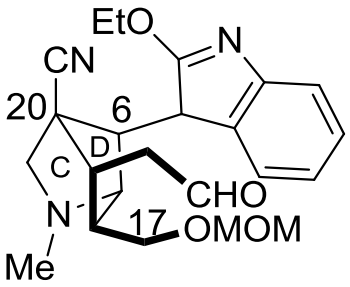
70%



90

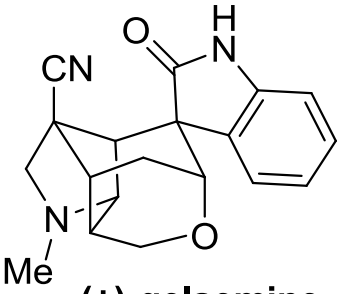
LDA

60%

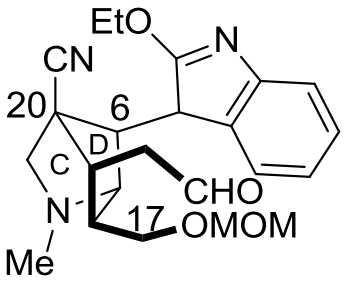


97

acid



(+)-gelsemine



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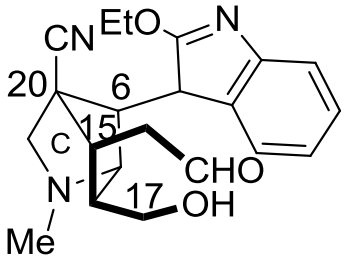
acid



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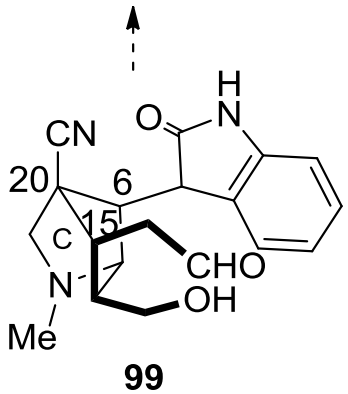
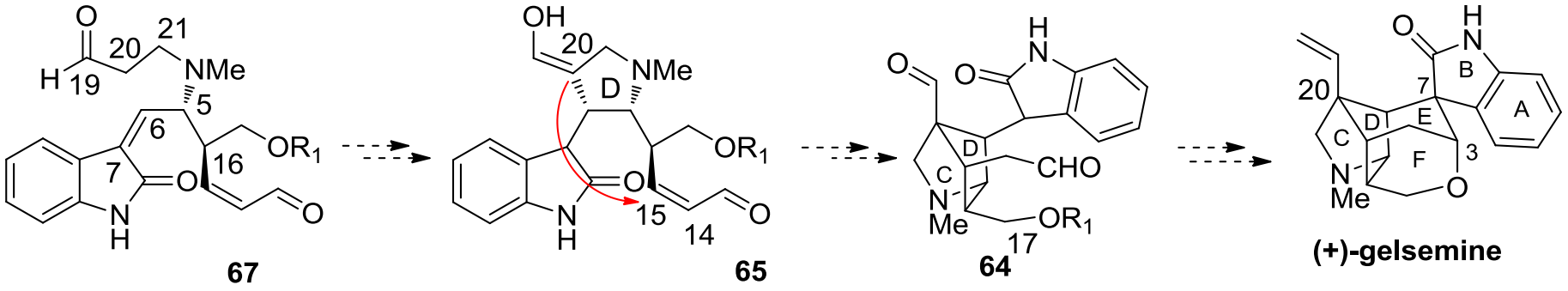
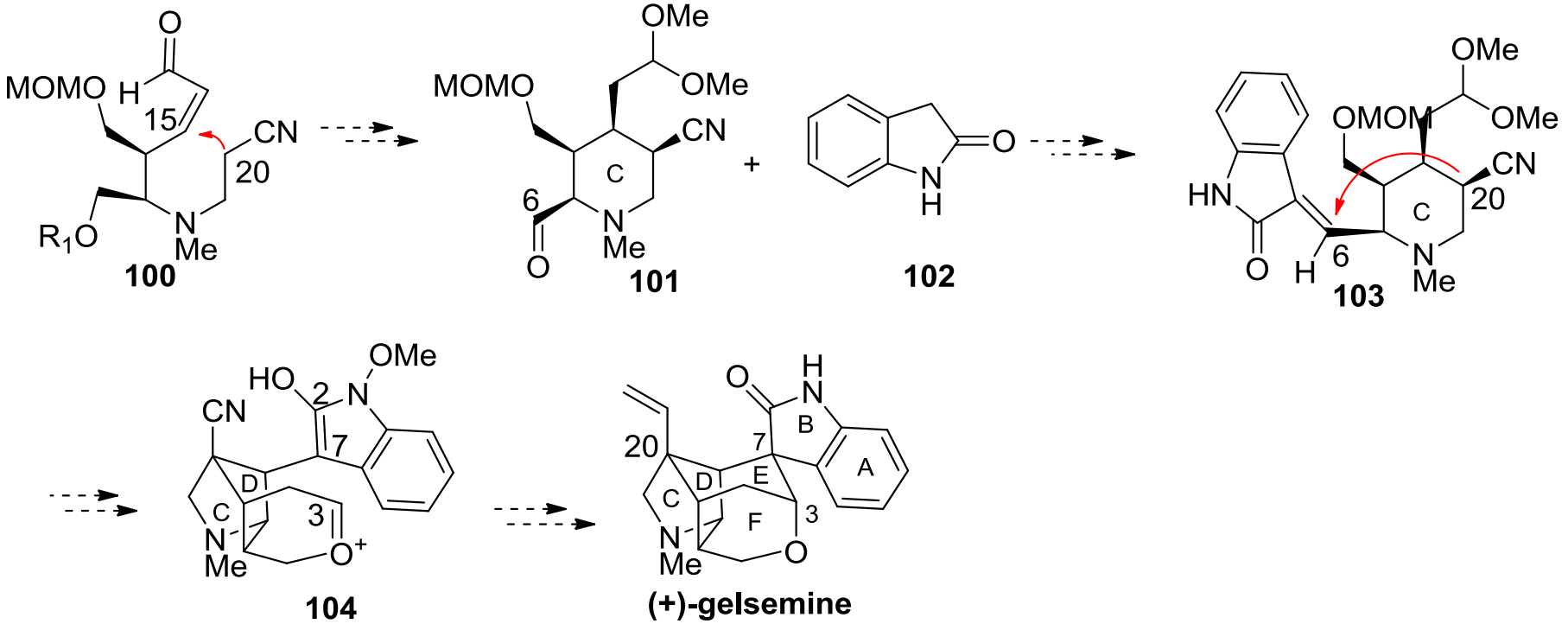


99

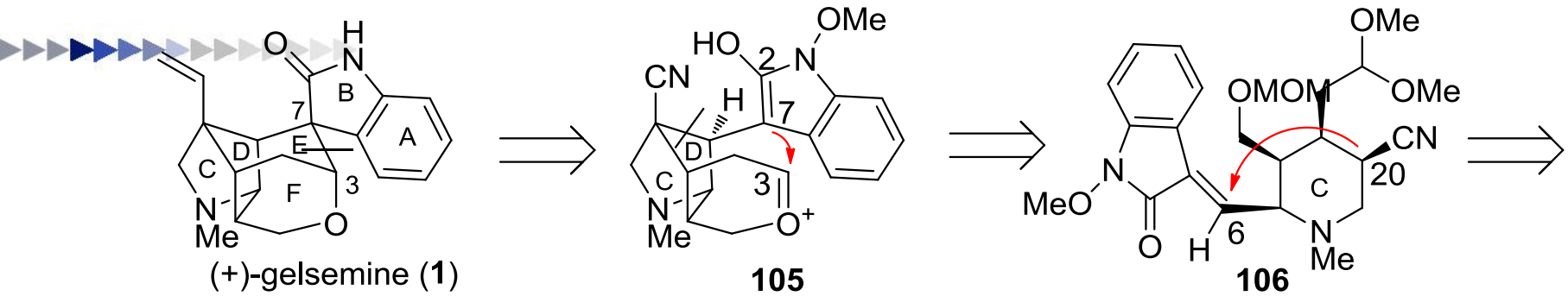
Initial synthesis strategy

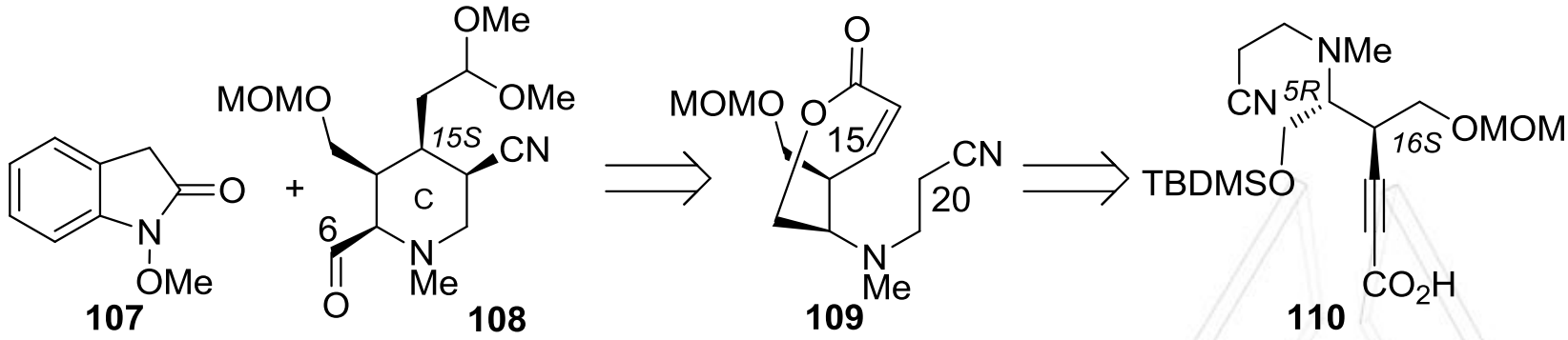


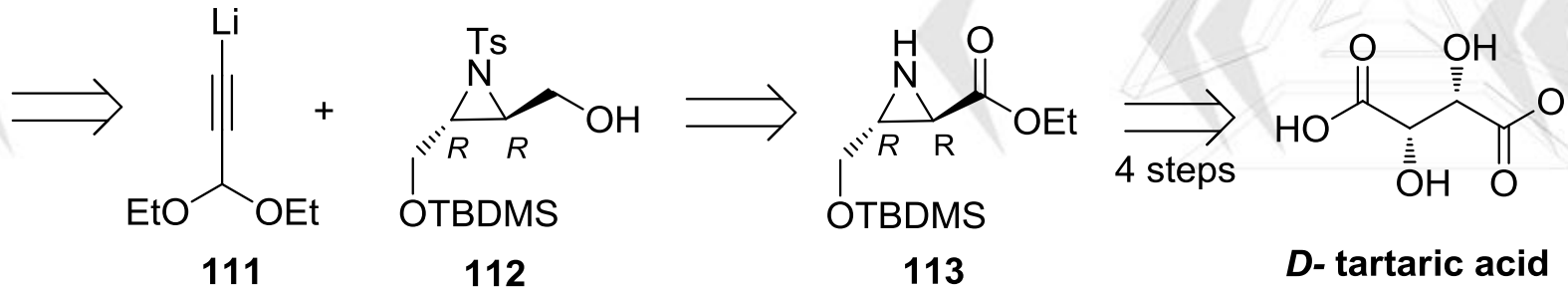
Adjust synthesis strategy



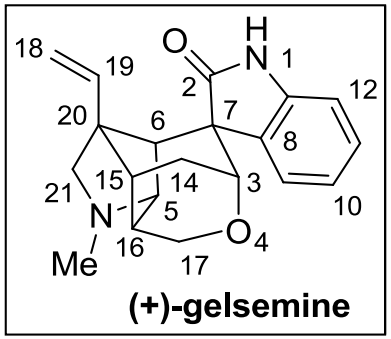
Retro-synthetic Analysis of (+)-Gelsemine

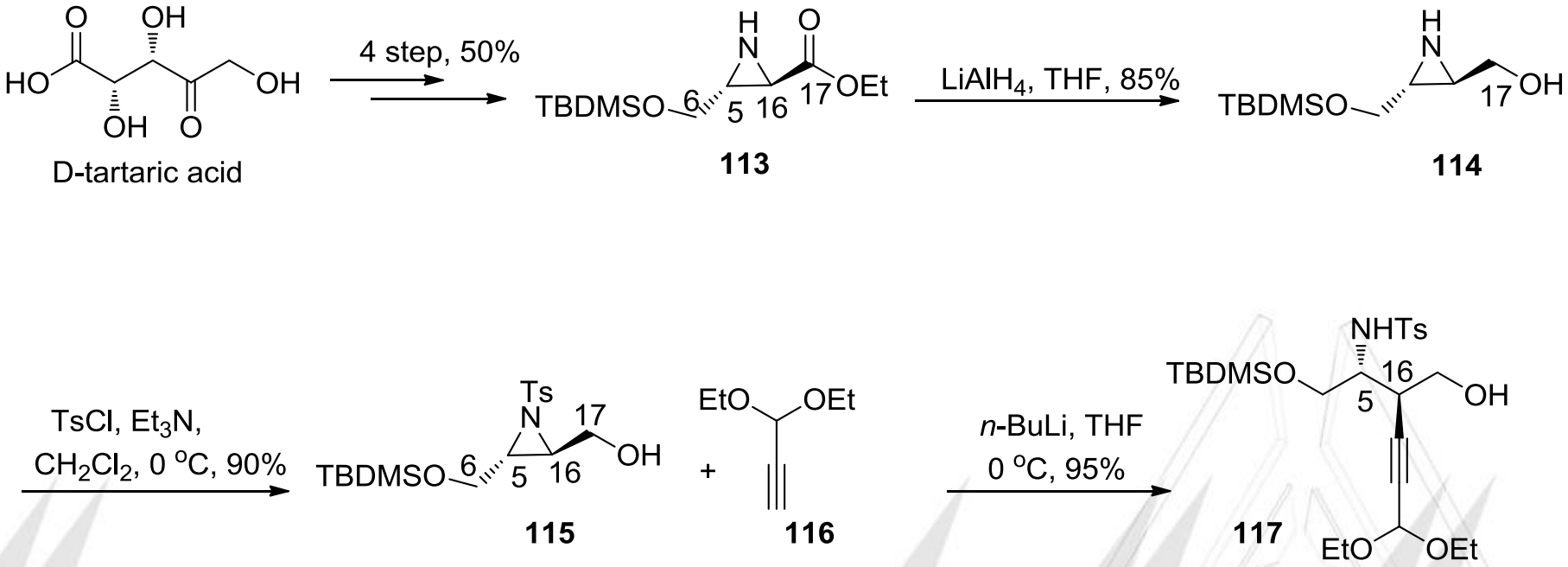






Constuction the C5 and C16 stereocenter of gelsemine

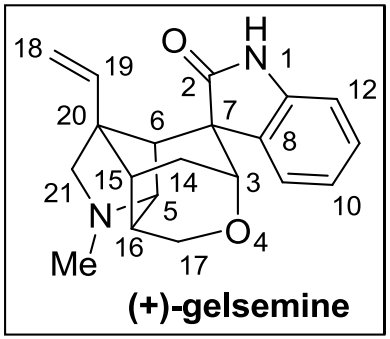


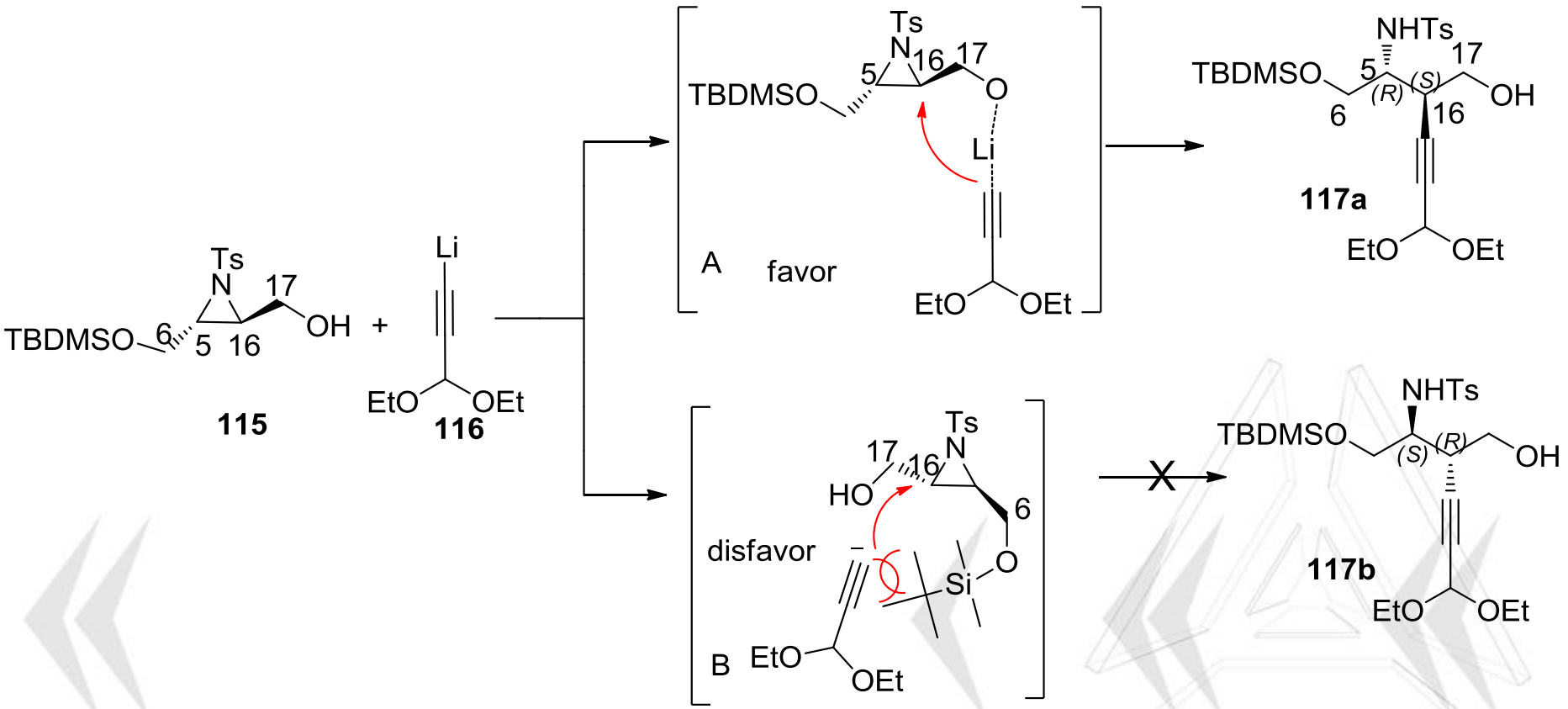


Hili, R.; Yudin, A. K. *J. Am. Chem. Soc.* **2006**, *128*, 14772

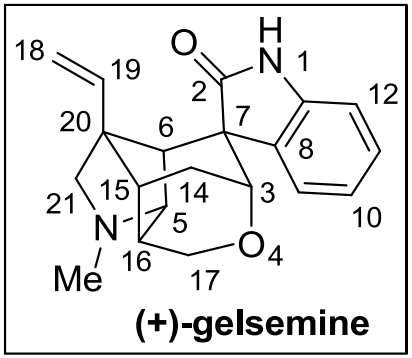
Fuji, K.; Kawabata, T.; Kriyu, Y.; Sugiura, Y. *Heterocycles* **1996**, *42*, 701

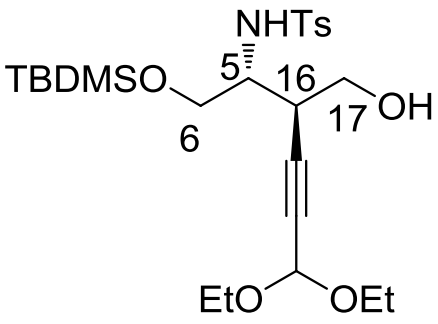
Region- and stereoselectivity addition of **116** to **115**





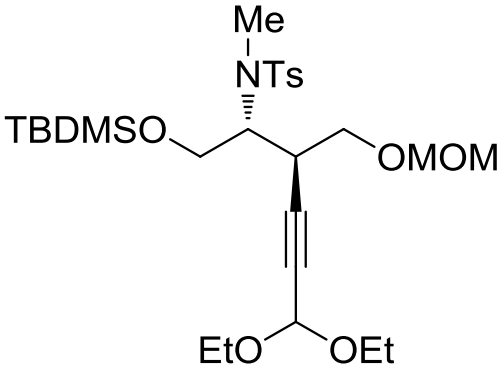
Total Synthesis of (+)-Gelsemine





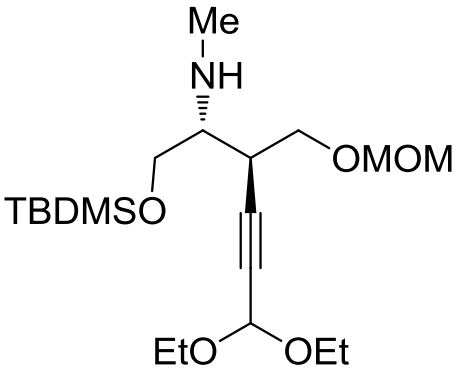
117

1) MeI, K_2CO_3, 98%
2) MOMCl, NaH, 95%



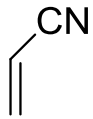
118

Mg, CH_3OH, 90%



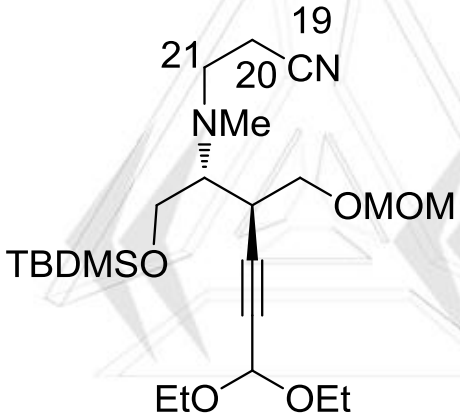
119

+



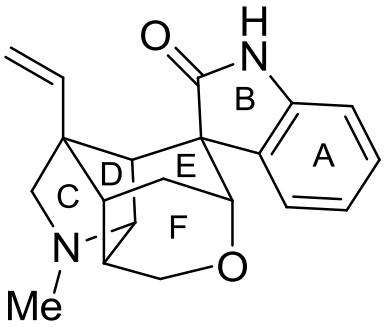
acrylonitrile

CH_3CN, reflux
95%

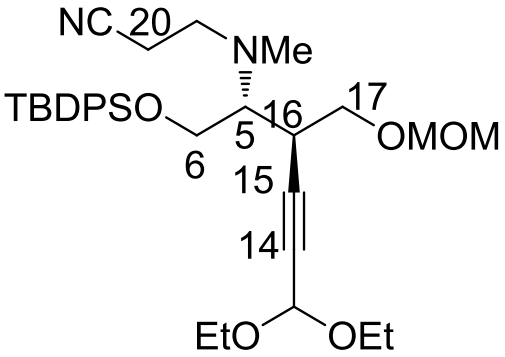


120

Construction the C-ring of gelsemine

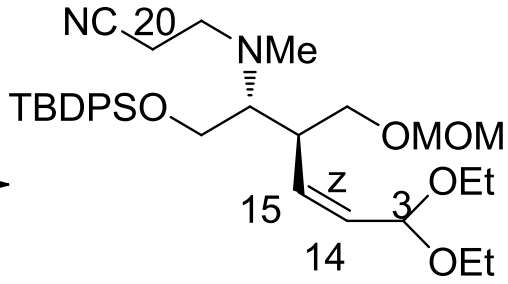


(+)-gelsemine



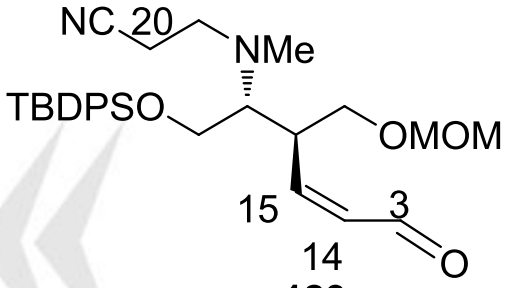
121

Lindlar Cat. H_2,
CH_3OH,rt
95%



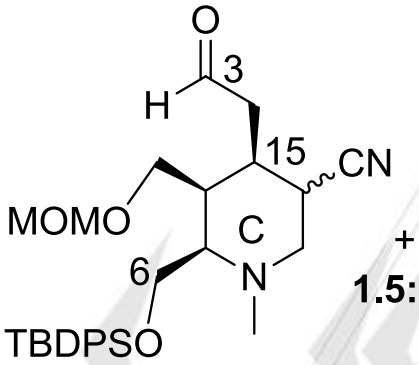
122

p-TsOH, CH_2Cl_2,
0^oC
85%



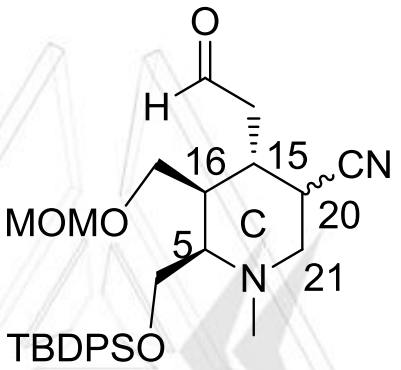
123

LiHMDS,THF,
-78^oC
70%



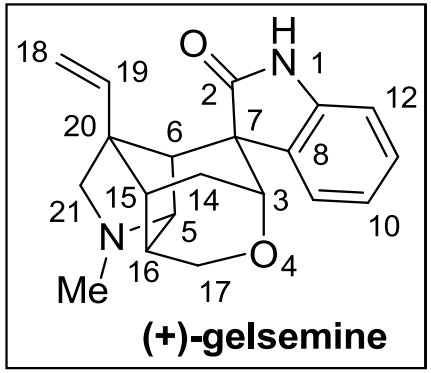
124

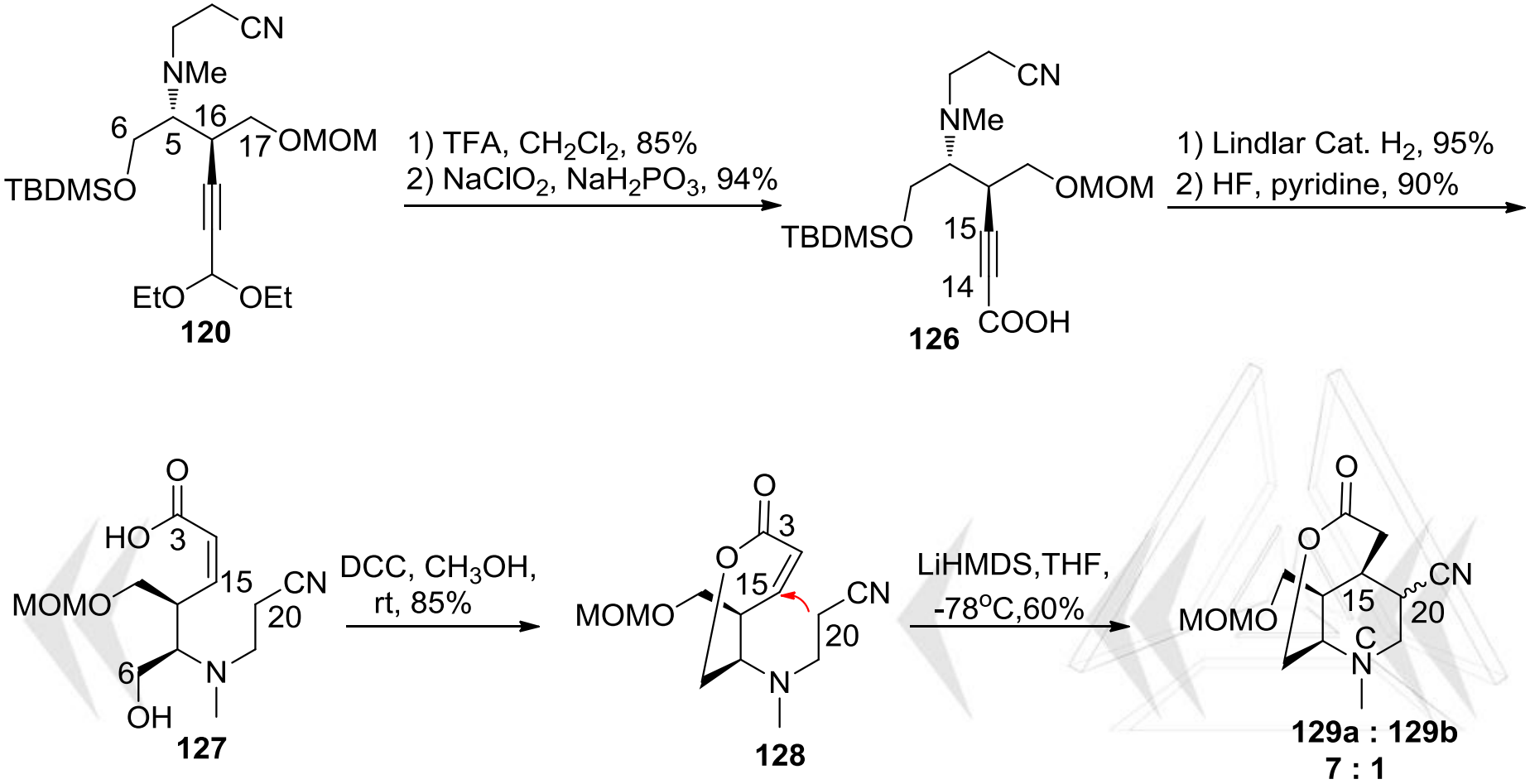
1.5:1



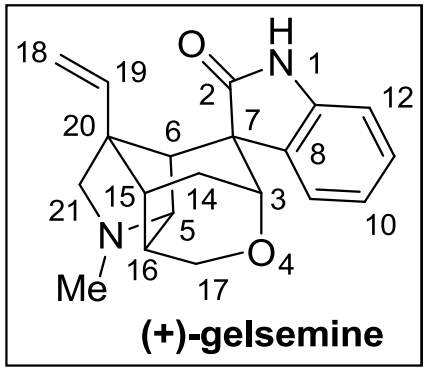
125

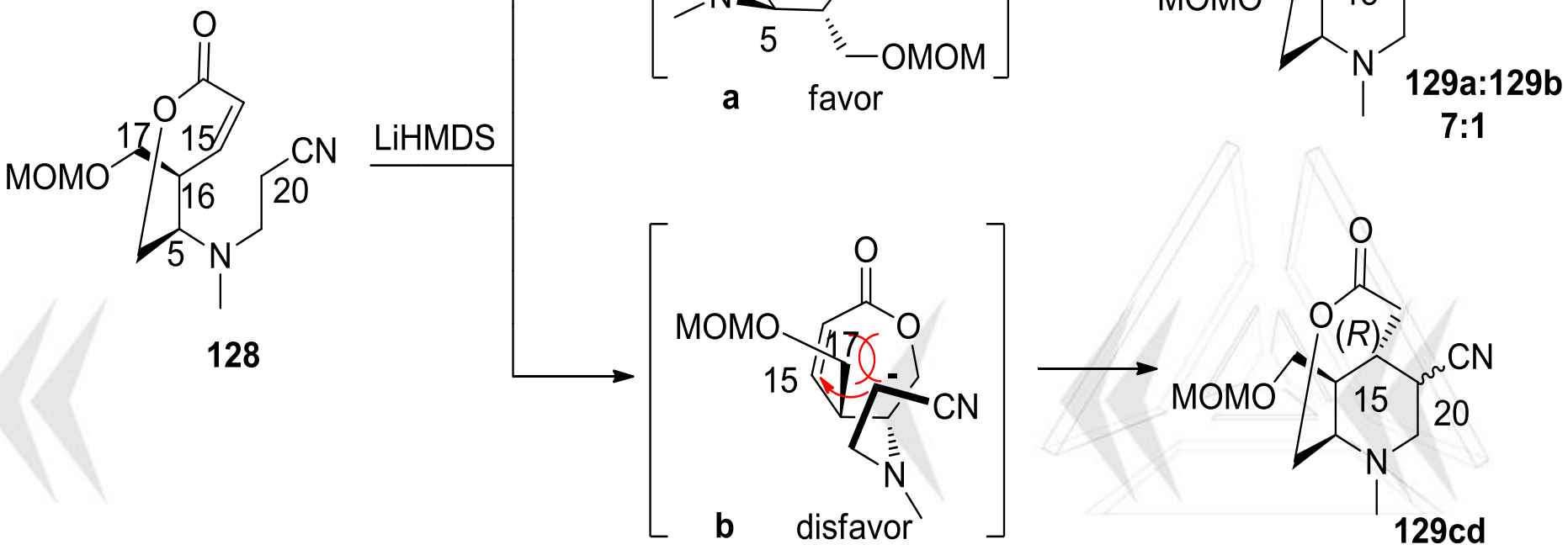
Stereocontrolled synthesis
C15 stereocenter



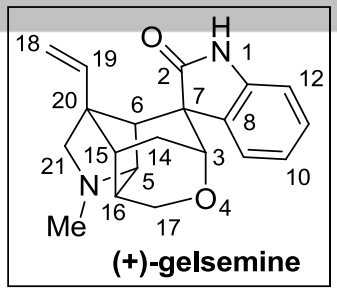


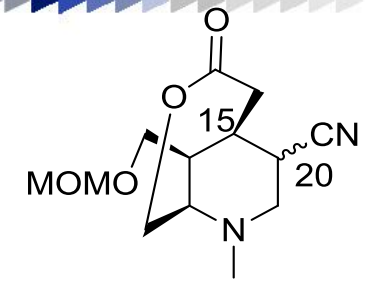
Stereocontrol synthesis
C15 stereocenter





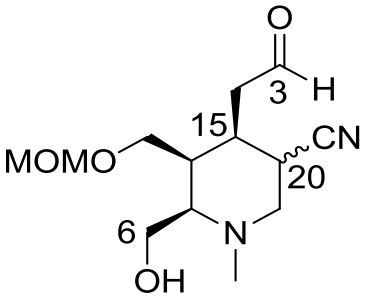
Total synthesis of (+)-gelsemine





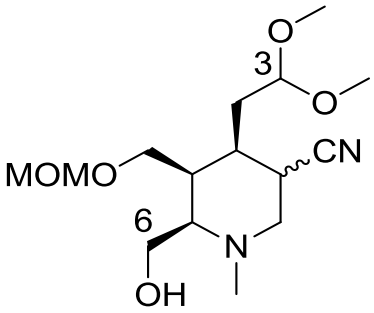
129a:129b
7:1

DIBAL,CH_2Cl_2,
-78°C
60%



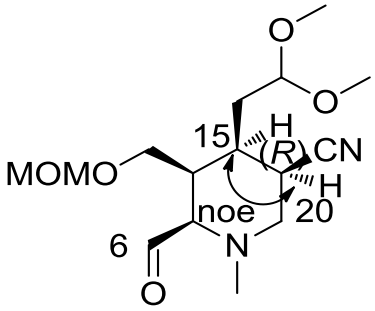
130ab

$HC(OMe)_3$
80%



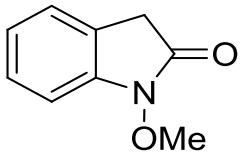
131ab

Swern oxidation
92%



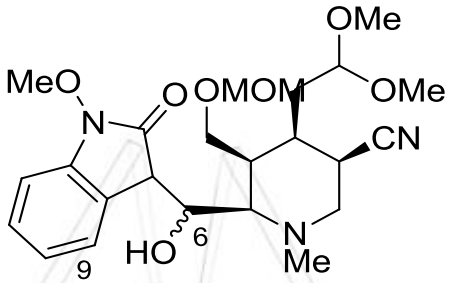
132

\+



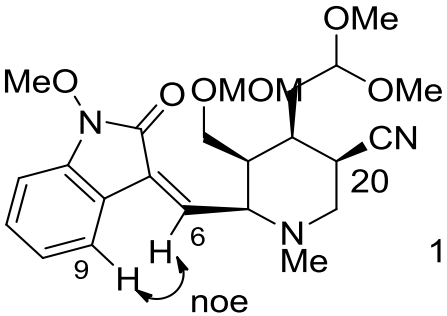
133

LDA



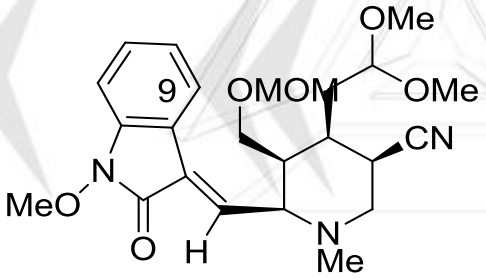
134

$SOCl_2$,pyridine
70% two step



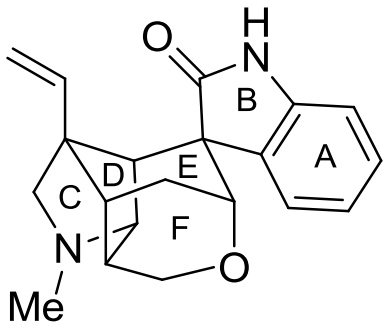
***Z*-136a**

\+
1.5 : 1

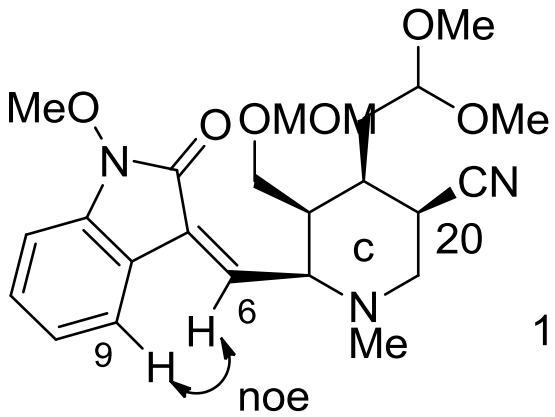


***E*-136b**

Construction the D-ring of gelsemine



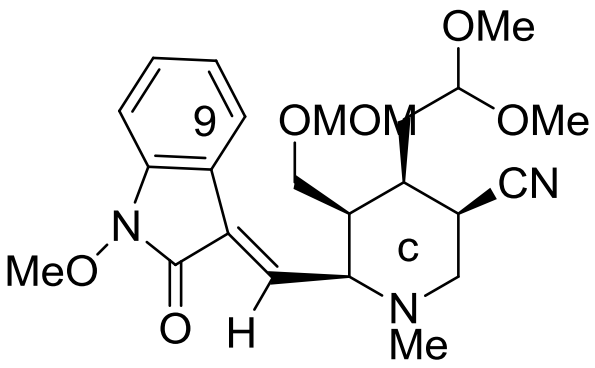
(+)-gelsemine



***Z*-136a**

\+

1.5 : 1

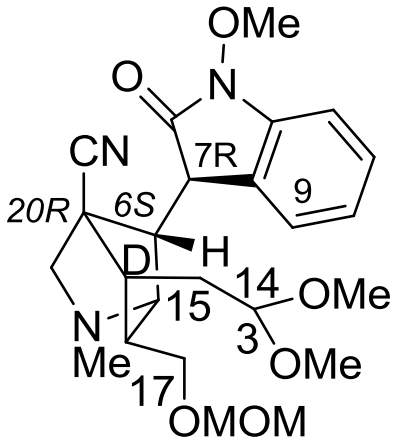


***E*-136b**

LDA, THF,

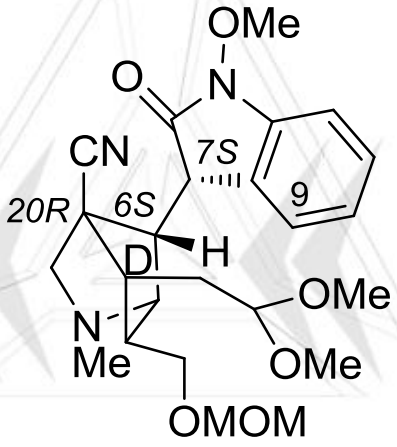
-78°C

75%



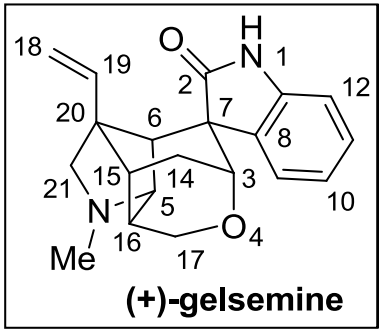
137a

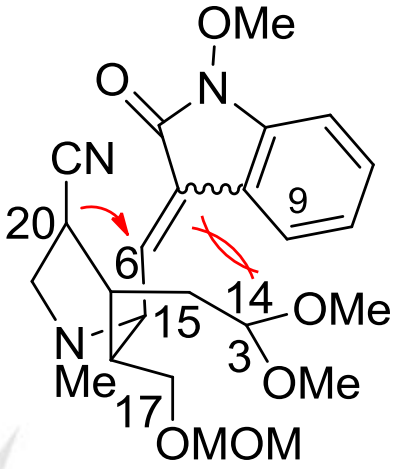
3 : 2



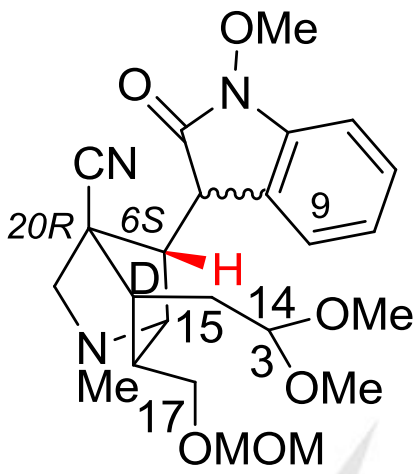
137b

Construction the C6 stereocenter of gelsemine



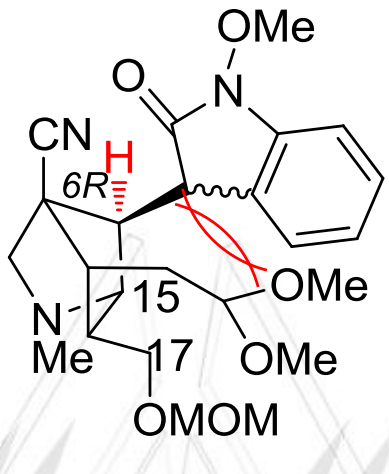


136ab



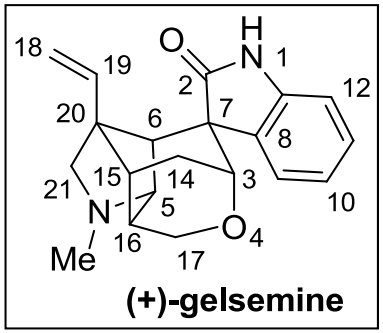
137ab

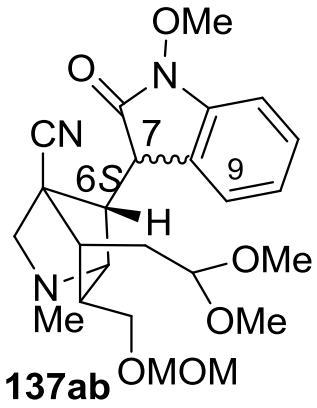
+



137cd

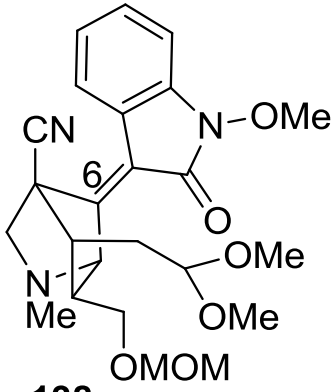
Total synthesis of (+)-gelsemine





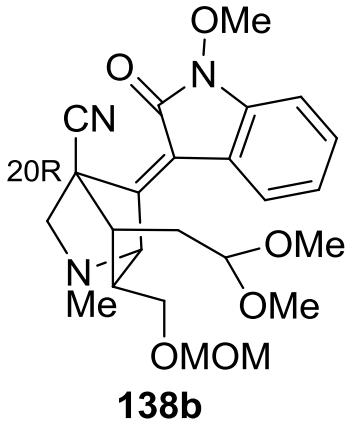
1) LDA, PhSeCl;
2) $NaIO_4$, $NaHCO_3$

70% yield for two steps



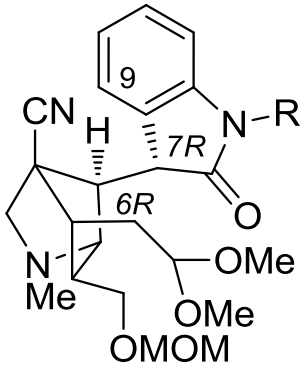
+

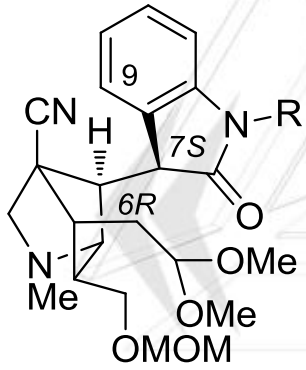
5 : 1



Lindlar cat., H_2, 90%

or 5% Pd/C, H_2, 98%



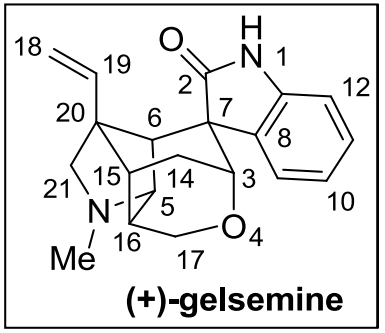


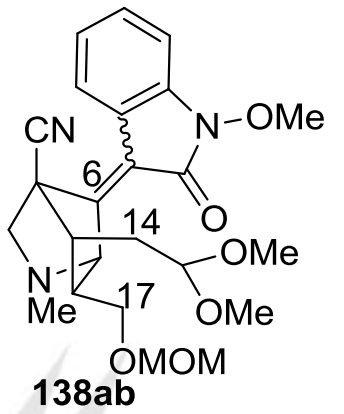
137c, R = MeO
139a, R = H

2 : 1
3 : 1

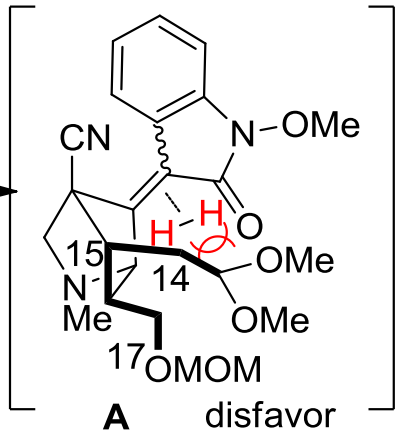
137d, R = MeO
139b, R = H

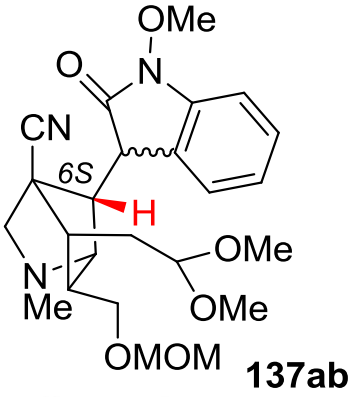
Total synthesis of (+)-gelsemine

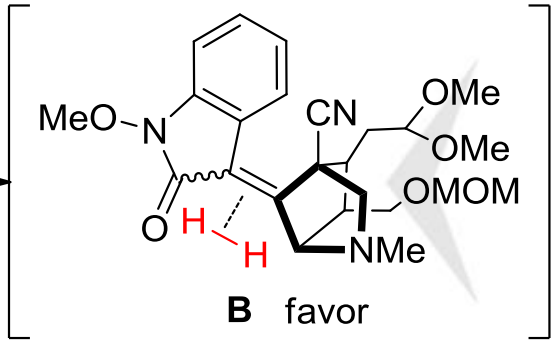


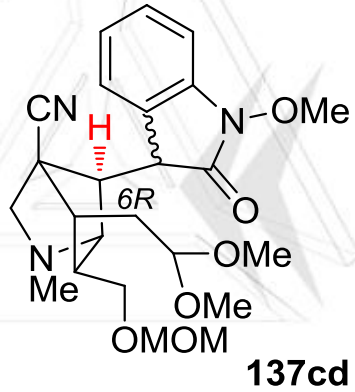


Lindlar cat.,
H_2, 90%

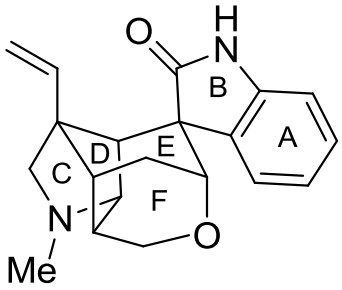




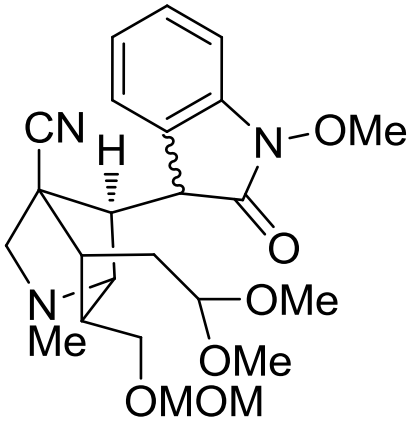




Total synthesis of (+)-gelsemine via enol-oxonium cyclization

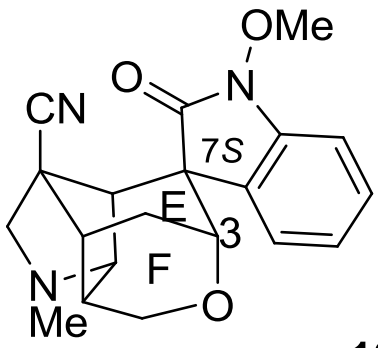


(+)-gelsemine



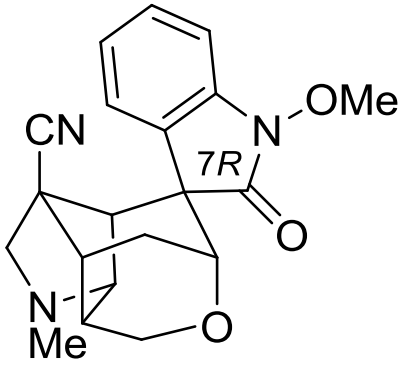
137cd

p-TsOH, $CHCl_3$, reflux, 73%



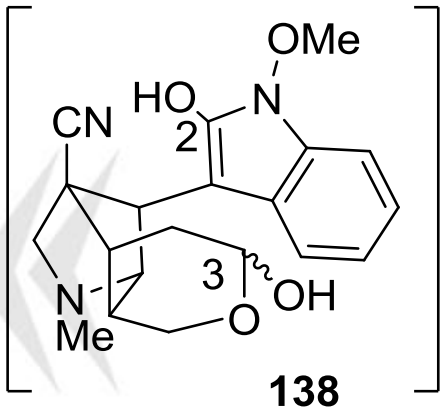
140a

10 : 1

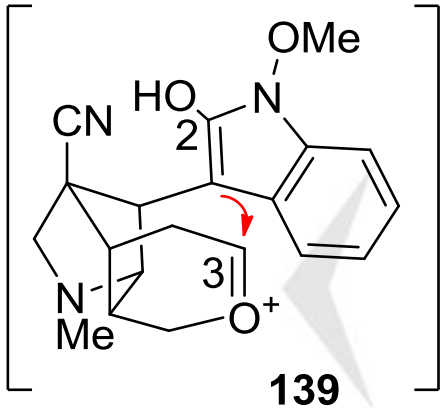


140b

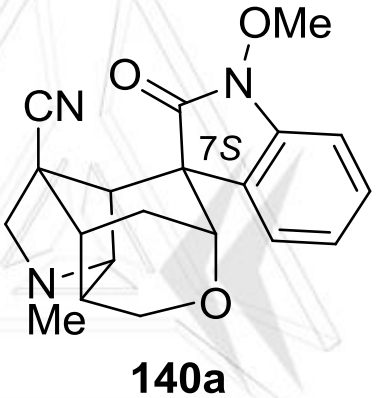
acid



138

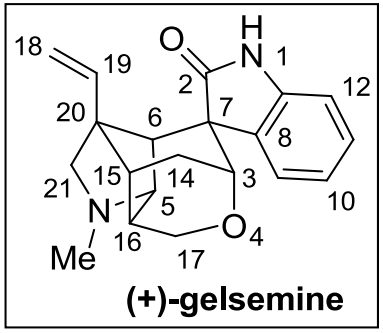


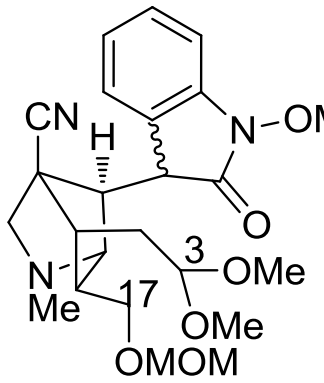
139



140a

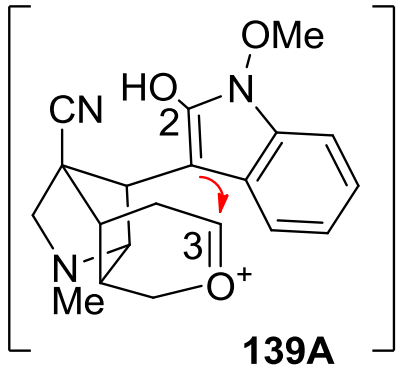
Stereocontrol synthesis
C7 stereocenter



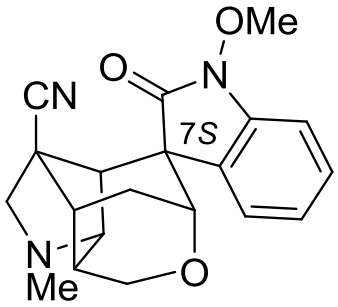


137cd

p-TsOH, $CHCl_3$,
reflux, 73%

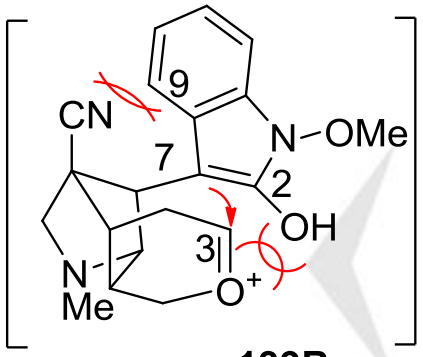


139A

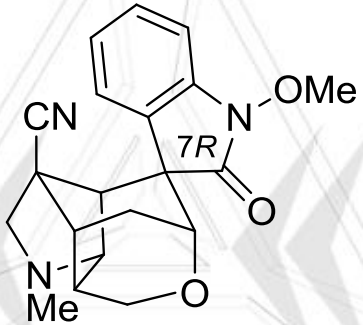


140a

10:1

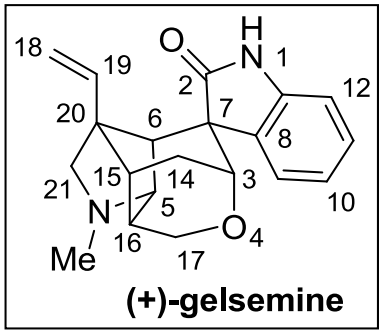


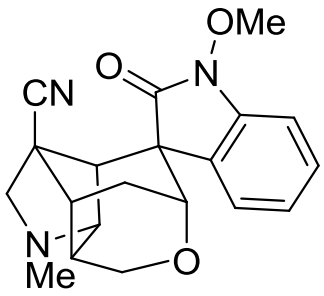
139B



140b

Total synthesis of (+)-gelsemine

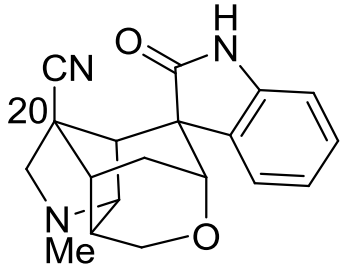




140a

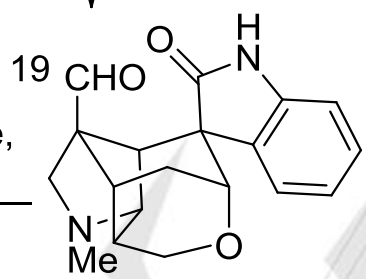
Pd/C H_2, MeOH

98%



141

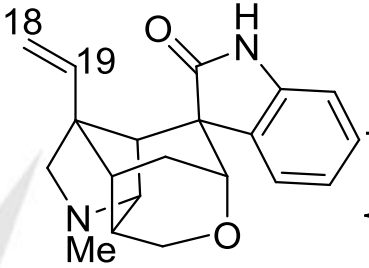
DIBAL-H,Tol,72%



142

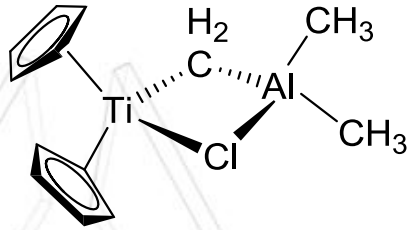
Tebbe reagent, THF, pyridine, reflux, 10 h

60%

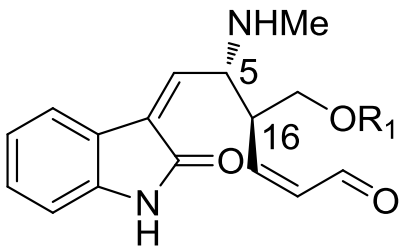


(+)-gelsemine

Tebbe reagent:

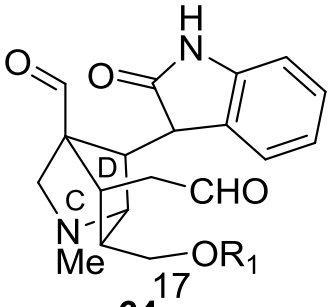


Summary



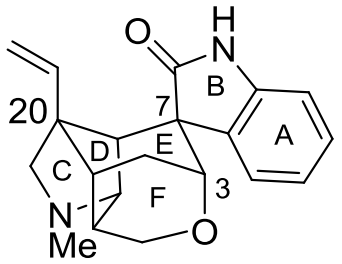
70

Org. cat

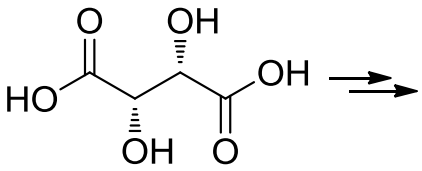


64

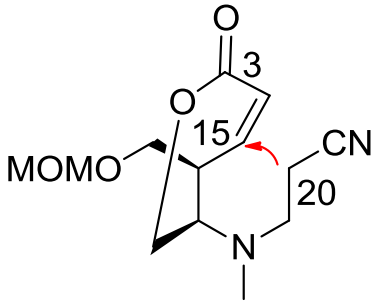
acid



(+)-gelsemine

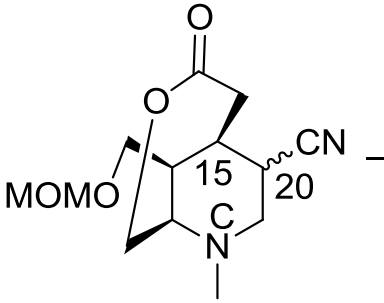


***D*- tartaric acid**

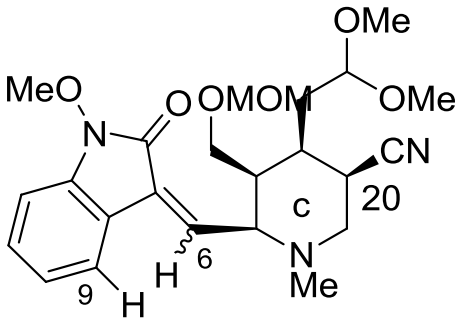


128

LiHMDS,THF,
-78°C,60%

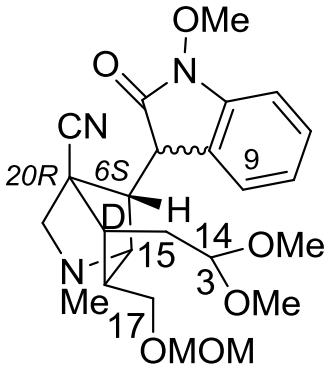


129a : 129b
7 : 1



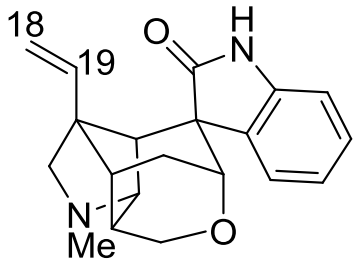
136

LDA, THF,
-78°C
75%



137

acid



(+)-gelsemine

25 steps with 1% overall yield.

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Thank you!
Happy holidays!